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INFANTILE SCURVY: THE BLOOD, THE BLOOD-VESSELS AND THE DIET*

ALFRED F. HESS, M.D., AND MILDRED FISH
NEW YORK

The following study considers infantile scurvy from a point of view which is somewhat unusual. Although it includes a chapter on diet, it is nevertheless chiefly concerned with scurvy as a hemorrhagic disease. This phase of the subject seemed worthy of investigation, as hemorrhage is the typical clinical symptom of scurvy, whether it manifests itself in bleeding into the gums, or as the equally well-recognized subperiosteal hemorrhages of the long bones. Indeed, some authors follow Barlow in considering infantile scurvy under the group of the hemorrhagic diseases, believing the hemorrhages to be the primary disturbance. There has been, however, as far as we know, no study of the blood in this disease, if we except some estimations, scattered through the literature, of the hemoglobin or of the blood-cells. We have devoted our attention especially to the question of the coagulability of the blood, with the object of ascertaining whether there is any marked change in this particular and whether a disturbance of this function can account for the various hemorrhagic symptoms. As it is now known that coagulation is closely associated with the platelets of the blood, an examination of these cells was also carried out. In addition a routine examination was made of the red and the white blood corpuscles and of the hemoglobin. In the course of this study our attention was gradually directed from the blood to the blood-vessels. We found it urgent to seek some means by which we could distinguish between hemorrhages due to a weakness of the blood-vessels and those which are the result of some defect of the blood itself.

As may be supposed, no intimate study of this kind could be pursued without having interesting clinical phenomena present themselves for consideration from time to time. We shall not, however, consider infantile scurvy from a clinical point of view, as the disease has been so frequently and thoroughly treated in all its symptomatology, but

* Submitted for publication Oct. 5, 1914.
* From the Research Laboratory, Department of Health, New York City.

shall merely discuss a few clinical phenomena which seem to be of interest. The same is true as regards diet. This question will also not be taken up in detail, but be discussed merely in some particular aspects. Our study in the main is based on numerous cases of scurvy which have developed in the past few years in the Hebrew Infant Asylum. We are dealing, therefore, with a group of institutional infants concerning whom we have clinical records for a long period previous to the onset of the disease, and whose welfare we have been able to follow for many months following their recovery. A number of these cases developed in the course of an attempt to dispense with the giving of orange-juice. In view of the fact that pasteurized milk is now heated to a temperature of only 145 F., which is claimed by many (including the commission on milk standards) not to destroy its chemical constituents, it seemed that infants should thrive on this milk without the addition of fruit-juices to their diet.

In obtaining blood for the tests of coagulability, about 5 c.c. was obtained from the jugular vein and allowed to flow into a 1 per cent. solution of sodium oxalate in the ratio of 1:10. In no case were coagulation tests made from blood obtained from the prick of a finger or the lobe of the ear; these methods cannot be relied on, as they introduce the disturbing factor of the thromboplastic substance of the tissue juices, and thus do not allow us to obtain an accurate estimate of the coagulability of the blood itself. The importance of this point may be realized when we add that the simple fact of not entering a blood-vessel at the first attempt, and in this way of introducing a minimal amount of tissue-juice into the aspirated blood, was found to invalidate our results. The oxalated blood was immediately centrifuged for fifteen minutes at high speed, and the plasma pipetted off for examination. The coagulation tests were carried out after the method suggested by Howell,[1] which is as follows:

Five drops of plasma are added to each of five small test-tubes. To these tubes increasing amounts (one to five drops) of 0.5 per cent. calcium chlorid made up in normal salt solution are added. The time is then noted when the plasma in the various tubes is firmly clotted. This time is designated as the coagulation time, and was noted in our records (Table 1) by a $+++$ sign. Lesser degrees of coagulation were marked $+$, which indicates the very faintest beginnings of coagulation, and $++$ which indicates a jellylike consistency of the clot.

In addition to these tests, a test was made for antithrombin in many cases. For this purpose, the plasma was heated to 60 C. in order to destroy the prothrombin, and was then filtered, in order to get rid

1. Howell, W. H.: The Condition of the Blood in Hemophilia, Thrombosis and Purpura, Arch. Int. Med., January, 1914, p. 76.

of the coagulated fibrinogen. One drop of this heated plasma was put into each of four tubes. To these tubes 1, 2, 3 and 4 drops, respectively, of thrombin was added. This thrombin was prepared from fibrin after Howell's method and was obtained in crystalline form. After the antithrombin and the thrombin had remained in contact for

TABLE 1.—RESULTS OF COAGULABILITY TESTS OF PLASMA (PROTHROMBIN)

Date	Name	$CaCl_2$ 0.5 % (drops)	Time of Coagulation (min.)*	Remarks
4/ 3	M. N. (scurvy).....	1	12	Infant has hemorrhage into the gums and petechiae on body.
		2	10	
		3	9	
		4	9	
		5	9	
	A. B. (normal).....	1	7	
		2	6½	
		3	6½	
		4	6½	
		5	7	
5 /4	M. H. (scurvy).....	1	15+	Infant has slight peridental hemorrhage and some petechiae.
		2	10	
		3	10	
		4	10	
		5	10	
	C. F. (normal).....	1	15+	
		2	15+	
		3	10	
		4	10	
		5	8	
	B. B. (scurvy).....	1	15+	Infant has swelling of femur.
		2	15+	
		3	12	
		4	8	
		5	8	
5/15	H. G. (scurvy)....	2	15+	A freshly made solution of calcium was used in this experiment.
		3	14	A mild case of scurvy.
		4	12	
		5	12	
		6	10	
		7	14	
	S. B. (normal).....	2	15+	
		3	10	
		4	10	
		5	10	
		6	6	
		7	10	
	H. C. (scurvy).....	2	15+	A mild case of scurvy.
		3	12	
		4	12	
		5	10	
		6	8	
		7	12	

* Five drops of oxalated plasma.

EPICRISIS.—In these tests the tube which first showed clotting should be taken as the standard, as it represents the optimal recalcification. It will be noted that coagulation was but slightly delayed in the cases of scurvy.

fifteen minutes, ten drops of a fibrinogen solution (made from cat plasma) were added and the time noted when coagulation occurred. In all these tests, whether for prothrombin or for antithrombin, control tests of normal plasma were carried out at the same time and under identical conditions.

Table 1 shows five tests of plasma from scurvy and three from control cases. It will be seen (Table 2) that two kinds of examinations were made; the one, which may be termed the coagulability test, includes the interaction of all the substances of the plasma, the prothrombin, the antithrombin, the calcium, the fibrinogen, etc., and the other, designated as the antithrombin test. Looking over Table 1 we

TABLE 2.—RESULTS OF EXAMINATIONS FOR ANTITHROMBIN

Date	Name	Thrombin (Drops)	Time of Coagulation (Min.)
4/3	M. N. (scurvy)	1	16
		2	4
		3	3
		4	3
	B. G. (child who frequently developed ecchymotic spots)	1	14
		2	5
		3	3
		4	3
	A. B. (normal)	1	20
		2	6
		3	5
		4	5
5/4	M. H. (scurvy)	1	26
		2	6
		3	6
		4	6
	C. F. (normal)	1	20
		2	6
		3	6
		4	6
	B. B. (scurvy)	1	14
		2	4
		3	4
		4	4

EPICRISIS.—Evidently the antithrombin is not increased in scurvy; further tests confirmed these results.

find that the plasma of the scurvy cases generally clotted more slowly than that of the controls; in other words, that there is a slightly diminished clotting-power of the blood in scurvy. This property, however, is not absolutely constant, and therefore not an essential manifestation of scurvy. To what constituent of the blood is this diminished coagulability to be attributed? A glance at Table 2 at once negatives the possibility that it may be occasioned by an increase of antithrombin. The tests were uniformly convincing in this regard. May it then be the result of a lack of prothrombin or a lack of calcium or a deficiency of both these essential factors of clotting?

The question of a deficiency of calcium in the blood is an interesting one, not only because this substance is of prime importance in coagulation, but in view of the fact that some have maintained, as we shall see, that the calcium content is decreased in the tissues in scurvy, whereas others have found it to be increased. Before discussing this question, however, let us consider the significance of these coagulation tests from this point of view. The addition of sodium oxalate to plasma prevents clotting, as is well known, by means of precipitating the calcium in the blood. It should be understood that in the ratio in which we have added it to the plasma, it is not sufficient to precipitate all the calcium in the blood, some calcium still remains in solution. This becomes evident if we compare the results of adding the usual strength (1 per cent. of oxalate) and twice this percentage to specimens of the same blood.

Table 3 reproduces an experiment of this kind. This table shows that although there is no difference as to time of clotting between the series to which 1 or 2 per cent. oxalate was added, there is marked difference between them as regards the tube in which the clot first occurred. In the tests in which 1 per cent. sodium oxalate was added, there was rapid clotting when 3, 4 and 5 drops of calcium solution were added to the plasma. On the other hand, where the plasma had been made with a 2 per cent. oxalate solution it required 5 drops of the calcium solution to recalcify the plasma sufficiently to bring about a clot; 3 or 4 drops of calcium were absolutely insufficient to bring about this result. In other words, the clotting-time remains unaltered in our tests whether we add more or less of the sodium oxalate solution; the only difference is that, if we add more oxalate, it is necessary to recalcify with a correspondingly greater number of drops of the calcium solution. There is one other physiologic fact which we must take into consideration in judging these coagulation tests, namely, that in the clotting of the plasma the amount of calcium necessary to produce a clot varies in direct ratio with the amount of prothrombin present. It is therefore not correct to consider these two factors separately — to

speak, for instance, of a deficiency of calcium; for it is only a relative deficiency that has any clinical importance. If the plasma is diluted to one-half, less calcium is required to produce a clot; if it is diluted to one-fourth, still less calcium is required. We shall not enter into the details of the experiments which demonstrate this interesting phenomenon, as we expect to report on it elsewhere in another connection.

With these facts before us as regards both the decalcification of plasma by oxalate and the interrelation of calcium to prothrombin in the clotting process of the blood, let us return to Table 1 and consider whether it can furnish any information as to a possible deficiency of

TABLE 3.—COAGULATION TEST OF PLASMA PREPARED WITH A WEAK AND A STRONG OXALATE SOLUTION

Date	Strength of Oxalate Added (%)	$CaCl_2$ 0.5 % (drops)	Time of Coagulation (min.)*	Remarks
6/26	1	1	36+	Both tests were made with the same specimen of blood.
		2	36+	
		3	7	
		4	6	
		5	6	
	2	1	36+	
		2	36+	
		3	36+	
		4	36+	
		5	6	

* Five drops of oxalated plasma.

EPICRISIS.—The strength of the oxalate solution does not affect the time of clotting, but does influence the amount of calcium which it is necessary to add in order to bring about coagulation. The calcium is therefore not entirely precipitated from the blood by the 1 per cent. solution.

these two substances. Although it does not enable us to state whether or not there is a slight decrease of prothrombin, it does enable us to judge whether or not a *relative* deficiency of calcium exists, that is to say, relative to the prothrombin. From a physiologic standpoint, as we have stated, this is the only type of calcium deficiency that is important — a condition of negative calcium balance, in which the calcium is insufficient to bind all the prothrombin, and in which, as a consequence, coagulation is retarded. Such a condition does not exist in infantile scurvy. *The slight defect in coagulability cannot be attributed to a relative insufficiency of calcium.* Had such been the case, we should have found it necessary to add an increased amount of calcium to the

plasma in scurvy cases as compared with the normal control; the clotting would have occurred in the tubes containing the larger amounts (five or six drops) of calcium solution. The tests show, however, that no increased addition of calcium was necessary. Whatever may be the finer physiologic cause, the slight defect in the clotting-power of the blood, which we have noted, plays but a secondary rôle in this disease; the characteristic hemorrhages are the result, as will be shown below, of quite a different pathologic condition.

A few simple tests of coagulation were made with unaltered blood. For this purpose ten drops of blood were dropped from the syringe into thoroughly cleaned, flat-bottomed test-tubes, 1.5 cm. in diameter, and the time of clotting ascertained. The normal coagulation time of blood tested in this manner is about six minutes. The tests of the blood of the scurvy cases varied between four and one-half and eight minutes and were therefore considered to correspond to the tests with plasma.

In addition to the coagulation-time of blood, the bleeding-time has been emphasized, especially by Duke.[2] This term refers to the time which it takes the blood to cease flowing after a puncture is made into the tissue. For this purpose a prick may be made in the lobe of the ear and the time noted when the blood ceases to flow. It is evident, according to what we have stated above, that a test of this kind includes at least two factors of coagulation, the coagulability of the blood as well as the thromboplastic substances of the tissues, and therefore that it is not identical with a test of the coagulation time of the blood or of the plasma. In two cases, one mild, the other pronounced, there was found to be a prolonged bleeding-time. The blood kept flowing from the puncture for fully five minutes and showed a deficiency in clotting. In other cases, however, in which the disease seemed equally advanced a prolongation of the bleeding-time was not met with, so that we must conclude that this abnormal condition may occur, but cannot be considered characteristic of the disease.

Table 4 shows the result of the examination of platelets. These tests were carried out by means of the staining solution recommended by Wright and Kinnicutt, the blood being obtained from the finger-tip. Although we were unable to obtain uniform counts from day to day, nevertheless the number of platelets was found in all cases to fall within normal limits. There was no marked decrease in the number of platelets such as has been described in connection with some hemorrhagic conditions and which might account for a tendency to hemorrhage. It will be noticed that in each case two counts were carried out.

2. Duke, W. W.: The Pathogenesis of Purpura Hemorrhagica with Especial Reference to the Part Played by Blood-Platelets, Arch. Int. Med., November, 1912, p. 445.

In other particulars the blood shows the changes which are commonly associated with secondary anemia (Table 4). There was a relative as well as an absolute deficiency in the hemoglobin, a slight decrease in the number of red blood-cells, occasionally the appearance of a nucleated red cell, and an increase in the number of leukocytes.

TABLE 4.—THE PLATELETS AND OTHER BLOOD-CELLS IN SCURVY

Name	Date	Platelets	Leukocytes	Erythrocytes	Hmgl. % (Sahli)	Remarks
M. H.	5/ 3	280,000	.....	.....	..	
	5/ 4	248,000	10,000	.....	..	
	5/ 5	.....	.....	.....	..	Boiled orange juice given.
	5/ 8	.....	.....	4,300,000	35	
	5/16	.....	15,900	.....	..	
	7/ 2	.....	6,800	5,456,000	40	Well but pale.
A. L.	5/ 3	300,000	.....	.....	..	
	5/ 5	.....	21,000	.....	..	
	5/ 9	.....	.....	5,480,000	..	
	5/11	382,000	.....	.....	..	
	5/13	.....	.....	.....	65	
	5/16	.....	11,500	.....	..	
H. C.	5/ 8	320,000	20,000	.....	..	
	5/ 9	.....	.....	5,340,000	..	
	5/13	.....	.....	.....	70	
	5/16	362,000	.....	.....	..	
B. B.	5/ 4	496,000	21,000	.....	..	A severe case.
	5/13	585,000	14,000	3,200,000	70	
	5/18	.....	17,600	.....	..	
	7/13	.....	40 000	7,672,000	82	Has gained well lately.
	7/15	.....	.....	7,640,000	88	
H. Y.	5/15	560,000	.....	.....	..	
	5/16	424,000	.....	.....	..	
	7/ 9	.....	.....	5,750,000	45	

It is impossible to state whether this moderate leukocytosis has any specific connection with the disease, or whether it is a reaction to some toxic substance existing in the circulation and should be brought into relationship with the slight febrile reaction which has been frequently noted to occur as one of the phenomena of infantile scurvy. In connection with these blood-changes we wish to call attention to the

regeneration of hemoglobin and of red cells during the convalescence of the disease. It will be noticed (Table 4) that in one instance there was an abnormal increase in the red cells (polycythemia), the count reaching over seven millions on two successive days.

THE BLOOD-VESSELS: CAPILLARY RESISTANCE TEST

What then is the cause of the bleeding which dominates the clinical picture of this disease? When it was found that the hemorrhages could not be accounted for by a defect in the clotting-power of the blood, we directed our attention to some disturbance of the blood-vessels. For the purpose of this investigation we devised a "capillary resistance test,"[3] which is carried out as follows:

A blood-pressure band is placed about the infant's arm in the usual manner. We made use of the Tycos apparatus for this purpose and raised the pressure rapidly until it reached the 90 mark. After the pressure had been maintained at this level for three minutes the band was removed, and when the blueness of the arm had faded an examination was made for petechial spots. The principle of this test is simple and must be evident at once. It consists merely in putting an excess of pressure on the capillaries and venules and observing whether the vessels allow the blood to escape readily. Ninety degrees pressure was selected as the optimum, because it was found that a less degree did not regularly produce venous congestion of the arm, which it is essential to bring about. In a few cases, due to an unexplained cause, there was an increase of arterial pressure reaching 100 or somewhat higher, so that raising the resistance to 90 did not produce cyanosis of the extremity; in a case of pertussis the pressure reached 125 when the infant cried. In such cases it was of course necessary to raise the pressure somewhat higher, as the entire test loses its efficacy if the return flow of the blood is not completely occluded. Numerous cases of scurvy were tested by this means and in addition, many normal cases served as control observations. It was found beyond question that the scurvy cases reacted abnormally. In these infants the forearm would show many petechiae; in some cases they were sprinkled over the entire surface whereas in normal infants they were almost always absent or there were but few to be seen.[4] In the case of an infant 18 months old, who developed a mild scurvy

3. Hess, A. F.: Proceed. Soc. Exper. Biol. and Med., 1914, xi, 130.

4. No importance should be attached to the petechiae which appear just below the pressure band, as these are found in most cases, normal as well as abnormal. After removing the bandage a sufficient interval should be permitted to elapse for the arm to assume its normal color so that the minute hemorrhages can be readily seen. Pressure tends to bring them out prominently. It is probable that the test can be carried out by simply applying a tourniquet for three minutes sufficiently tight to cause venous congestion but not to obliterate the radial pulse.

in spite of receiving vegetables, the test was negative; in all others it was positive, and persisted in some instances after all definite symptoms had disappeared. Where an eruption, such as eczema or prurigo was present on the forearm, the petechiae developed especially at the site of the lesions.

The capillary resistance test is brought forward not as a specific test for scurvy, but rather as a method of bringing to view a weakness of the vessel walls whatever may be the cause. We have found it to be positive in various cases of toxemia, and it will no doubt be found to be present wherever the vessel walls are weak; for example, in some of the purpuras which occur more frequently in adult life.

In connection with scurvy a study of petechiae is of the greatest interest. In our experience they have been present very frequently in the earliest stages of the disease. It is probable that their presence has not been emphasized in descriptions of this disease because they have not been sufficiently sought for. This year we had an exceptional opportunity of investigating this sign, as well as other early symptoms of the disease, when, as stated above, we were making observations on the group of infants fed with milk which had been subjected to a moderate degree of temperature. As may be imagined, not only were petechial spots sought for almost daily, but all other early signs of disturbance of nutrition were examined for with regularity. In adults in the course of various purpuras, superficial petechial spots are found especially in the skin of the lower extremities. This can probably be explained by the fact that these vessel-walls give way as the result of the increased pressure of gravity, brought about by the standing posture. We should naturally expect the distribution of petechiae in infants to be somewhat different on account of their horizontal posture. Such proved to be the case. Petechiae were most frequently seen on the upper part of the back and neck, and on the chest, and more often on the upper than on the lower extremities. There was, however, no part of the body that can be said to have been entirely spared. They were found in the mucous membrane of the hard and soft palate, and also in several instances on the palpebral conjunctiva, appearing just as they do so typically in cases of bacterial infection of the blood. It is probable that we must consider the blood in the urine, especially the minute hemorrhages which can be detected only by microscopic examination, merely as an evidence of petechiae into the internal organs. Post-mortem examinations show the same wide distribution of small hemorrhages. In almost all cases they have been found in the pleura, peritoneum, pericardium, in addition to the large extravasations which are found beneath the periosteum.

Beside the petechial hemorrhages, we must consider edema as being typical of an increased permeability of the vessel-wall. In scurvy we

frequently find not only petechiae but also edema. Edema of the eyelids and of the ankles is well known as a clinical manifestation of the scurvy of infants as well as of adults. Post-mortem examinations also confirm the increased permeability of the vessels in this regard; fluid is commonly found in the pleural, the peritoneal, and the pericardial cavities, as well as a marked increase of fluid (noted on incision) in the subcutaneous tissues.

A comparison of scurvy and hemophilia from this point of view brings out a striking contrast. In hemophilia we do not find petechial spots scattered over the surface of the body, nor is edema a symptom of the disease. On applying the "capillary resistance test" in cases of hemophilia—we have tested three cases of this disease by this method—it is found that petechiae are not induced by this increase of intravascular pressure. In other words, in hemophilia the vessels seem to be normal. The clinical symptoms of the two diseases bring into sharp relief this distinction in the pathogenesis of the hemorrhages. In scurvy the hemorrhages are generally minute and numerous; in hemophilia the hemorrhages are few and extensive, because when the blood does escape from the vessels an excessively large amount is poured out owing to its defective coagulability. We shall not, however, enter on this subject in greater detail, as it will be considered in the future as a study of hemophilia.

When one makes a subcutaneous puncture, for example, into the abdominal wall, in the case of an infant suffering from scurvy, it was found that very often a small hemorrhage develops at the site of the puncture wound. This is not the case when one makes a hypodermic or subcutaneous puncture in a normal person. It was thought that this observation might be of value in distinguishing early cases of scurvy, and, in fact, the first tests carried out with this object in view promised well for this method. In this case (that of an infant, 6 months old, admitted to the asylum in the spring of 1913) puncture tests of this kind resulted in a hemorrhagic reaction; as soon as orange-juice was given the reaction ceased. More extensive trials with this puncture test, however, showed it to be unreliable. This is due partly to the fact that although a minute hemorrhage occurs, it does not always appear at the surface, but is concealed beneath the integument. Notwithstanding the fact that subcutaneous puncture cannot be relied on for diagnosis, it is of interest to note the difference between the reaction to this simple procedure of normal infants and of those afflicted with scurvy; it may prove to be of diagnostic value when hemorrhage results. Possibly it is merely an evidence of increased bleeding-time, or the subcutaneous tissues as well as the vessels may be involved in this disease.

CLINICAL OBSERVATIONS

In a consideration of scurvy the period which may be termed prehemorrhagic or prescorbutic is the most important. By this is meant the time when the first nutritional changes take place and before the diagnosis can be made. This interval varies in length according to individual susceptibility and according to the diet which the infant received. In our cases it varied from about four to seven weeks. This prescorbutic period, during which scurvy is latent, frequently passes unnoticed and indeed in many cases does not furnish any sign or symptom whatsoever by which it can be recognized. The question also may be raised as to just when scurvy can be considered cured, and whether there is not a postscorbutic latent period. Are we to consider an infant who has had scurvy normal, as soon as all the signs and symptoms of illness have disappeared? It is probable that although the symptoms of scurvy disappear with almost miraculous rapidity within even a few days of the administration of orange-juice or fresh vegetables, many of the cells of the body do not become normal for a far longer period. This conclusion would follow from the fact that when we apply the capillary resistance test to infants who have had scurvy, we find that they react positively, that the vessels show an abnormal permeability, for some weeks after all symptoms have disappeared. Again, a case such as the following leads us to this opinion:

J. H., April 19, 1913, showed signs of scurvy; the left femur was swollen and tender, also the tibia. There was swelling of one eyelid. These symptoms developed in spite of the fact that breast-milk had been given for eight days previously. On April 19 orange-juice was given. Although the swelling and the tenderness of the bones rapidly disappeared and the child gained in weight and appeared well, it again developed (on May 9) a hemorrhage over one eyelid.

In other words, although the child seemed to be absolutely well, there evidently was still a tendency to hemorrhage. Furthermore, the liability to recurrence or to relapse in scurvy would suggest that the tissues do not return absolutely to the normal state, although this might also be interpreted as evidence of a susceptibility on the part of the individual infant. In the literature recurrences are mentioned as occurring very exceptionally. This view is probably based on the fact that following the development of scurvy, all precautions are taken to prevent a recurrence. During the last few years we have observed two instances in which infants have twice had scurvy; indeed, it seems logical to suppose that, given favorable conditions, a second attack will occur. The following is a case in point:

Infant 6 months old, weighing 10½ pounds in September, 1913, developed swelling above and below the knee, accompanied by marked tenderness. It had been getting Schloss milk for one month. When lemon-juice was given and

the food changed to two-thirds pasteurized milk and one-third barley-water with sugar, the symptoms rapidly disappeared. The lemon juice was discontinued at the beginning of January. Six weeks later tenderness of the lower extremities was noted and a hemorrhagic reaction to subcutaneous puncture. In addition to the milk, the infant had received cod-liver oil and phosphorus for three weeks. Hemorrhage of the gums developed some weeks after this. At the time of the first attack of scurvy, the infant was 6 months old and weighed 10¼ pounds; at the time of the second attack it was 11 months old and weighed 14½ pounds.

Although we do not wish to consider the symptomatology of scurvy, as it has been thoroughly portrayed so often, nevertheless we shall devote a few words to the all-important subject of the early symptoms. We have had an exceptional opportunity to observe the disease from this point of view, especially during the past year where, for a time, we were watching a group of infants to ascertain whether they would show any scorbutic signs on discontinuing the giving of fruit-juice. Writers on this subject have described various symptoms as constituting the earliest signs of the disease. Our experience in this regard has been as follows:

In many cases we found the petechial spots, referred to above, as the first evidence of incipient scurvy; the classical tenderness of the extremities was very often called to our attention by the nurse; in other instances the pallor of the infant led to the diagnosis of scurvy. This peculiar pallor has been noted by many observers and has been attributed by some to a loss of blood due to the hemorrhages. This correlation, however, does not seem to exist. The case among our series which had the greatest amount of hemorrhage, a true hematuria, nevertheless did not show marked pallor. It is probable that the loss of color is due rather to some disturbance of nutrition. Loss of appetite occurred early in some cases, but was not a constant feature. In others marked sweating was noted. English authors have laid especial emphasis on the early occurrence of red blood-cells in the urine. In view of this opinion especial attention was given to this point, to determine whether it constituted a reliable sign of the onset of this disease. It was, however, found quite inconstant. In several cases frequent examinations were made of centrifugalized specimens of the urine and no red cells whatsoever found, although at this time there was typical hemorrhage into the gums. In numerous instances we could observe no sign previous to these hemorrhages into the gums, occurring where teeth were present or were about to erupt. In some of these cases the hemorrhage into the gum was posterior to the teeth, and could be seen only when the mouth was wide open. Hemorrhages frequently can be artificially produced by sharp rubbing of the gums, a little expedient which will be found to be of diagnostic value in some cases. The distribution of the hemorrhage depends merely on chance circumstance.

For example, it seems reasonable to ascribe the fact that the subperiosteal hemorrhages involve the femur most frequently, to the frequent handling of the thighs in the course of the diapering of the infant. As has been stated above, almost any region may be involved in the hemorrhage. Not infrequently it may develop over the skull-bones. Finkelstein mentions that hemorrhage has been found post mortem in the dura mater. In one of our cases (L. S.) in which convulsions supervened in the course of the disease, the blood-tinged cerebrospinal fluid led us to believe that we were dealing with a case of this nature. This paragraph may be summarized by stating that there is no symptom which can be considered as preeminently the primary sign of scurvy; each varies in its time of appearance. *We would, however, add to the category of early signs of this disease the development of numerous petechial spots.*

According to our experience, the infectious diseases, including the prevalent infection termed "grip," do not play an essential rôle in the production of infantile scurvy. In 1912 a very severe and extensive epidemic of this infection spread through the infants' ward at about the same time that numerous cases of scurvy developed, but a careful analysis showed that there was no relation between the two diseases. It is probable, however, that any disturbance which decreases the vitality tends in a measure to the development of scurvy. Many of our patients had rickets as well as scurvy. The question of the interrelationship of these two diseases has been discussed pro and con since scurvy was first described by Barlow. In the statistics compiled by the American Pediatric Society, 45 per cent. of the scurvy patients suffered from rickets. In both cases of recurrence of scurvy which occurred in our wards it should be noted that rickets was also present.

Although the relationship between rickets and scurvy is questionable, there is another disease or diathesis which we believe to be definitely associated with the incidence of infantile scurvy. We refer to the condition described by Czerny as "exudative diathesis," a term which implies a predisposition to develop exudations into the skin or the mucous membranes; prurigo, "milk crust," some cases of eczema, recurrent bronchitis, etc., are some of the numerous manifestations of this congenital condition. It is generally agreed that a predisposition to scurvy exists, that although a large number of infants may receive the same diet only a few develop scorbutic symptoms. This has also been our experience in the infant asylum. Closer investigation revealed the fact that *almost all the cases that developed scurvy had exudative diathesis;* this was true in ten of the twelve cases, and in the two exceptions our records are incomplete in this regard. The association was so evident, that we have no hesitation in considering that there is

a close inter-relationship between the two conditions, that *exudative diathesis implies not only a diathesis for exudations, but also for the development of scurvy.* It is impossible to state whether this clinical relationship is one of summation or whether the two pathologic states are dissimilar, the exudative diathesis merely rendering the tissues more vulnerable toward scurvy. In this connection it is probably not without significance that the blood-vessels in exudative diathesis also show a decided weakness, an increased permeability, as judged by the capillary resistance test; petechiae can be produced by pressure in such cases not only during the scurvy, but to a less degree long after the scorbutic symptoms have disappeared.

In order to test the vital activity of the cells in scurvy the Schick test was carried out on six patients. This test consists in injecting intracutaneously 0.1 c.c. of a 1:10,000 solution of diphtheria toxin. In four patients ranging in age from 8 to 13 months there was no reaction; in other words, a sufficient amount of diphtheria antitoxin had been elaborated in the body to neutralize the toxin which was injected; in two cases the reaction was positive. From these tests it would seem that in spite of the marked nutritional changes, the cells are able to elaborate some of the important immune bodies. It would seem that in this disease the functions of certain cells are affected far more than those of others. For instance, the very changes so typical in the bones are brought about by the association of a lack of functioning of the osteoblasts combined with a normal activity on the part of the osteoclasts.

DIET

The infants in the group which we are particularly considering were being fed on various preparations of milk, and their diet was in no wise changed, excepting, as has been stated, that an attempt was made to do without orange-juice. Most of them were receiving mixtures of milk and barley water, the milk being "Grade A Pasteurized," that is, heated for thirty minutes to 145 F. Some were receiving malt soup, others Schloss milk and a few Eiweissmilch. It is interesting to note that all four children who were being fed on malt soup developed scurvy; this may have been mere chance, as these infants all had exudative diathesis, but can also be accounted for by the fact that in the preparation of this food the milk had been heated twice, the pasteurized milk having been brought to the boiling-point. As Neumann pointed out, this two-fold heating probably plays an important rôle in the production of scurvy. It is also possible that the malt should not be disregarded in this connection. Whether cereal, which was used in the form of barley-water, tends to the production of scurvy has never been definitely determined. This point must be borne in mind, how-

ever, in view of the classical paper of Holst and Froelich[5] on experimental scurvy produced by the giving of cereals, and on reflecting how large a part proprietary foods played in the statistics of the American Pediatric Society. As regards the cases which developed on an Eiweissmilch diet, little need be added. This is not a criterion of the efficacy or usefulness of this food, which was devised not as a permanent diet, but as a therapeutic agent.

During the past three years we have had a considerable number of cases of scurvy develop in infants being fed on pasteurized milk. In 1912, when the first cases were noted, we were pasteurizing the milk in our own diet kitchen, heating it to a temperature of 165 F. for twenty minutes. At this time several cases of scurvy developed, owing to the fact that through an oversight orange-juice was not given. During the past year we have been supplied by one of the large dealers with a pasteurized milk that has been heated only to 145 F. for thirty minutes. Nevertheless, we had several cases of scurvy develop on this diet. In most of the cases the infant was receiving two-thirds milk and one-third barley-water, with the addition of sugar. In two instances, whole milk was being given without the addition of barley water. There were other patients in the same ward on the identical diet who did not develop scurvy. In other words, the pasteurized milk was not the sole factor in the production of the disease. That the pasteurization did play an important rôle, however, was shown by substituting raw, unheated milk for the pasteurized milk, the formula and the amount of food remaining unchanged. In this case the scorbutic symptoms began to disappear within a week of giving raw milk and had altogether vanished in two weeks. Whatever the predisposing factor of scurvy (this infant had exudative diathesis), a case with this clinical course can be interpreted only as being, in a large measure, the result of pasteurized milk.

Raw cow's milk must not, on the other hand, be considered as having potent antiscorbutic properties. Its effect cannot be compared to the miraculous change which is brought about by giving orange-juice. This is especially striking when we take into consideration the small amount of orange-juice necessary to bring about a cure and compare it with the large amount of raw milk which is given. Raw milk, however, contains sufficient of the essential substances to prevent the development of scurvy.

It is possible that in addition to the pasteurization there are other factors in connection with the milk which enter into the causation of scurvy. Plantegna has laid emphasis on the freshness of the milk

5. Holst, A., and Froelich, T.: Ztschr. f. Hyg. u. Infektionskrank., 1912, lxxii, 1.

both before and after pasteurization. This factor may be found to resolve itself into a question of reaction, of greater or less acidity, which experiments on animals have shown to be of importance. Against the justification of attributing scurvy to the heating of milk, the favorable statistics given by Variot and other French authors, including thousands of cases of infants fed on boiled milk, have always seemed conflicting evidence. Whatever may be the explanation of their results, it must be remembered that these statistics refer to patients treated in the dispensaries, and that they were not observed under ideal conditions. There can be no doubt that milk loses some of its antiscorbutic qualities as the result of heating; pasteurized to the degree which we are considering, 145 for thirty minutes, it seems to lose only a portion of its essential properties. The cases that developed in our wards on this diet were for the most part very mild. They showed petechial hemorrhages, some tenderness of the bones, a very slight degree of peridental hemorrhage, but they did not evince a tendency to progress. There seems to have been almost, but not quite, a balance between the demands of the body and the supply in the diet of the essential substances on which scurvy depends. They were not all, however, of this mild or immature type of case; two of the severest cases developed in infants receiving two-thirds pasteurized milk.

DIETETIC THERAPY

We have come to a consideration of dietetic treatment, which at once suggests the efficacy of orange-juice. Last year we gave, as routine, orange-juice that had been boiled for five or ten minutes and found that we were able to obtain satisfactory results. One ounce was given daily and, as far as we could judge, boiling did not lessen its therapeutic value. This year, for orange-juice we substituted the juice of orange-peel, which was prepared as follows:

The orange-peel was finely grated and 1 ounce of it was added to 2 ounces of water, a small amount of sugar being added to overcome the slightly bitter flavor. The juice of orange-peel seems to serve the same purpose as the juice of the orange itself. It is being used at the asylum at the present time, and after a trial of several months, we have come to the conclusion that it has marked antiscorbutic power. At first we made use of the peel to test its value, but have continued its use because it allows us to serve the oranges to the older children in the institution, and in this way is somewhat economical.

According to our experience, the efficacy of vegetables cannot be compared to that of orange-juice. Two cases of scurvy developed among the infants over one year whose diet included vegetables, mainly carrots. It is impossible to state how much vegetable the nurses gave

these two children; there is no reason to believe, however, that they received less than the twenty-eight other children in the ward. It is probable that they had a peculiar susceptibility to scurvy; one had exudative diathesis. When we reflect that sporadic cases of beriberi have been reported in which vegetables had been given that had been cooked for a long time, we must consider whether it is not possible that vegetables may also lose their antiscorbutic properties if cooked to a high degree. The experiments of Holst and Froelich[5] would also seem to caution us in this regard; they found that the juice of white cabbage lost its antiscorbutic value when heated even to 60 C. for ten minutes.

One of the patients, an infant receiving malt soup, developed scurvy in spite of the fact that it was given a teaspoonful of cod-liver oil three times a day for one month before the disease manifested itself. It will also be noted that in the case of recurrent scurvy which we cited, the patient had been receiving cod-liver oil for some weeks previous to the onset of the second attack. Evidently this valuable therapeutic agent cannot be relied on as an antiscorbutic. This is of interest in view of the experiments of Osborne and Mendel[6] showing the ability of cod-liver oil to promote growth in rats which had been stunted by means of a standard diet. Olive-oil certainly does not possess any antiscorbutic power. In the severest case of our group the patient had obtained a teaspoonful of olive-oil three times a day for a month before the development of scurvy.

The potency of potato was tried in some cases. It will be remembered that, in the scurvy of adults, the value of potato has been greatly lauded, and that epidemics of this disease have been reported to have followed a failure of the potato crop. First we made some trials with potato flour which is sold in the market; this was prepared with water and added to the milk in the same proportion as barley-water. It was soon evident, however, that potato flour cannot cure scurvy. We next employed mashed potato; a tablespoonful of boiled potato was added to a pint of water, using for this purpose the water in which the potato was boiled. In other words, instead of using a tablespoonful of barley to a pint of water, mashed potato was substituted. This was found very efficacious. The scorbutic symptoms quickly disappeared, although it did not seem to bring about the sudden change that is sometimes seen when orange-juice is given. It is probable that baked potato is just as valuable as an antiscorbutic.

In view of what has been outlined, at what age should we begin to give infants an antiscorbutic? There is no doubt that if an infant is fed solely on heated cow's milk the tissues begin to lose antiscorbutic substances — there is a negative balance of this material — from the

6. Osborne, T., and Mendel, L. B.: Jour. Biol. Chem., 1914, xvii, 401.

very first days of life. Such being the case, it would seem that these essential substances should be supplied to the infant as soon as it is possible. As far as is known, there is no physiologic reason why orange-juice or potato should not be given in small quantities to an infant a few weeks of age. Two years ago, it was clearly shown[7] by means of an examination of the duodenal contents, that starch-splitting ferments are present in the intestine of infants at birth, and are secreted in large measure after the first few weeks of life. It would also seem worthy of trial to substitute potato water for barley-water in the mixtures of pasteurized milk which are being distributed with such great benefit by the various diet kitchens in the larger cities. This will obviate the necessity of constantly admonishing the mothers not to omit orange-juice from the daily diet of their infants.

COMMENT

The chemical processes involved in scurvy are as yet unknown. There have been a few metabolism experiments connected with this disease, but they do not agree in their results. Lust and Klocman[8] found a positive balance of mineral salts in the course of scurvy and a negative balance during convalescence. They describe a disturbance of elimination of the salts of the body, which is quite the opposite to what is found in rickets.

A more recent study of metabolism is that of Bahrt and Edelstein[9] which is based, not on examinations during life, but on chemical analysis of the organs after death. These authors found a decrease of ash in the bones, especially of calcium and phosphorus very much as in rickets. A test of this nature, of the organs of the body, ought to afford reliable information. It should be noted, however, that in the case in question the patient had been under treatment for six weeks prior to death and that the tissues may therefore not have been in the active stage of the disease at the time of death. Further tests must decide which of these views is correct; from a clinical point of view, it is difficult to associate a marked deficiency of calcium salts with a disease in which fracture of the bones is a classical symptom, followed by a normal formation of callus. It should be emphasized that metabolic studies of this kind at present are necessarily incomplete, that after the various salts and organic substances are quantitatively analyzed, there is no doubt that more substances have been omitted than included in the chemical tests. This disease, furthermore, sharply emphasizes the fact that although an estimation of the caloric value

7. Hess, A. F.: The Pancreatic Ferments in Infants, Am. Jour. Dis. Child., October, 1912, p. 205.
8. Lust, F. and Klocman, L.: Jahrb. f. Kinderh., 1912, lxxv, 663.
9. Bahrdt, H., and Edelstein, F.: Ztschr. f. Kinderh., 1913, ix, 415.

of food is important, it may omit the very substances which are essential to health and life. In some of our cases the caloric value of the food was as high as 120 calories per kilo, body weight, but nevertheless there was a development of scurvy, accompanied by loss of weight and failure of nutrition.

In this connection we must mention the very interesting and suggestive studies of Funk.[10] This author has coined the word "vitamines" for substances which are essential to the health and life of the body, and the lack of which produces a group of diseases which he has termed the "avitaminosen," including beriberi, scurvy, pellagra and rickets. The vitamines, Funk asserts, are crystallized nitrogen containing bodies of very complicated structure which are chemically defined, but concerning the exact structure of which we as yet know little. They are essential to life, although present in very small amounts. Such is the definition which Funk gives of the substances which he considers play an important and even vital part in nutrition.

Similar studies have been made by others, notably Stepp,[11] who terms these substances "lipoids," by which he means substances soluble in alcohol and in ether. He also found that animals could not live when deprived of these substances. Although these "vitamines" have not been satisfactorily isolated from a chemical point of view, and exception has therefore been taken to the term, there is no doubt from experiments on animals that these substances play an important rôle in the nutrition of the body. When they are removed from the diet the animals develop various nutritional disturbances, and regain their normal condition only when they are again added to the diet. These vitamines are thermolabile and are supposed to constitute a group of which there are various members. It is probable that one of this group is the vitamine which prevents the development of scurvy. It would also seem that this material is supplied in the mother's milk, and that this accounts for the fact that nursing infants do not develop scurvy.

SUMMARY

Infantile scurvy is a disorder characterized clinically by hemorrhage, for example, the classical bleeding into the gums and the subperiosteal hemorrhages of the long bones. A study of the cause of this bleeding, which must include a consideration of the clotting-power of the blood, forms the nucleus of this investigation.

For the coagulation tests blood was aspirated directly from the blood-vessels and oxalated. This plasma showed a slight diminution in clotting-power. This defect did not seem, however, to be the result of an insufficiency of calcium. The antithrombin was not increased.

10. Funk, C.: Die Vitamine, 1914, J. F. Bergmann, Wiesbaden.
11. Stepp, W.: Deutsch. med. Wchnschr., 1914, No. 18, p. 892.

Small amounts of blood were also obtained by puncture of the finger. Examinations of this blood revealed a normal number of blood platelets. In other respects the picture was that of a simple secondary anemia, except that the hemoglobin was diminished out of proportion to the red blood-cells. A marked regeneration of these cells during convalescence, leading to a polycythemia, was also noticed.

These various departures from the norm are insufficient to account for the hemorrhages associated with the disease. The integrity of the blood-vessels was therefore investigated by means of a device which may be termed the *"capillary resistance test."* This test consists in subjecting the capillaries and vessels of the arm to increased intravascular pressure, by means of an ordinary blood-pressure band, and of observing whether this strain results in the escape of blood through the vessels — the appearance of petechial hemorrhages into the skin. The vessels of normal infants were found to withstand, without apparent disturbance, 90 degrees of pressure for three minutes, whereas the vessels of infants suffering from scurvy gave way under this pressure. The test is not specific for scurvy, but is a method of demonstrating a weakness of the vessel walls, whatsoever may be its cause.

In the course of an exceptional opportunity to observe scurvy in its incipiency, numerous petechial hemorrhages of the skin or mucous membranes were frequently noted as one of the earliest signs of the disease; no sign, however, should be regarded as preeminently the primary symptom of scurvy.

It is generally recognized that scurvy has not only an exciting cause, but a predisposing cause. *The well-known "exudative diathesis" of Czerny was found definitely to predispose to the development of scurvy.* Whether there are other predisposing factors remains to be determined.

Several cases of scurvy developed in infants who were being fed on milk which was pasteurized to 145 F. for thirty minutes. They were cured by receiving fruit-juices or raw milk.

Orange-juice was found not to lose its efficacy as the result of being boiled for ten minutes. The juice of the peel was successfully substituted as an antiscorbutic for the juice of the orange.

Potato proved to be an excellent antiscorbutic. It is suggested that it be added to pasteurized milk as potato-water instead of the barley-water which is now commonly used as a diluent. In this way the necessity will be obviated of giving orange-juice.

Cod-liver oil or olive-oil, although given for weeks, did not prevent the development of scurvy.

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INTERNAL HYDROCEPHALUS

AN EXPERIMENTAL, CLINICAL AND PATHOLOGICAL STUDY *

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Part 1.—Experimental Studies

1. INTRODUCTION

The term "hydrocephalus" is merely a symptomatic designation for an idiopathic disease. The subdivisions into acute and chronic, internal and external, congenital and acquired, are made according to no one standard, but according to several — pathological, clinical and embryological. Such subdivisions do not clarify the pathogenesis, but serve to obscure it. Chronic internal hydrocephalus, whether congenital or acquired, is the most important and frequent form encountered.

Internal hydrocephalus is characterized by a progressive accumulation of cerebrospinal fluid in the ventricles, causing their dilatation and a consequent cortical atrophy and, when possible, enlargement of the head. The disease is usually fatal; spontaneous recovery, however, does occur in a small percentage of cases.

Numerous forms of treatment have been suggested and tried, but, as the number of methods indicates, they have been almost uniformly unsuccessful. The etiology being so obscure, any treatment is necessarily empirical and consequently unsatisfactory. Successful therapy must depend on the identification and the treatment of the cause of the disease.

It is evident that internal hydrocephalus is due to an abnormality either in the formation or in the absorption of cerebrospinal fluid or possibly in both. Our studies — experimental and clinical — have been concerned with the development, the pathology and the diagnosis of internal hydrocephalus.

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* From the Departments of Surgery and Pediatrics of the Johns Hopkins University and Hospital. A preliminary communication of this study appeared in the Journal of the American Medical Association, 1913, lxi, 2216.

2. HISTORICAL

Reference to hydrocephalus is made by the earliest medical writers. Hippocrates is credited with suggesting surgical treatment by trephining the anterior part of the skull. He evidently thought that the accumulation of fluid was extracerebral.

Galen was the first to give special consideration to this disease, which played a conspicuous part in his theory of the "animal spirit." Galen was really advanced in his knowledge of the anatomy of the ventricles of the brain. He thought they were in free communication with one another and that they formed a closed system. He knew of the aqueduct of Sylvius and of the foramina of Monro. Galen, however, believed that the soul or "animal spirit" was contained in the ventricles and that here it underwent a process of purification; the purified products were supposed to pass into the pores of the brain and the waste products found their way through the pituitary body and were discharged into the nose as "pituita." He considered hydrocephalus due to some defect in this process of elaboration of the "animal spirit."

The teachings of Galen were accepted without question until Vesalius, in 1543, denied the existence of the "animal spirit." Following Vesalius a succession of distinguished anatomists have been interested in the study of hydrocephalus. Among them have been Willis, Sylvius, Rhazes, Celsus, Petit, Pacchionis, Brunner, Littré, Morgagni, Cotugno, Monro, Haller, Robert Whytt, and in the nineteenth century Magendie, John Hilton, Luschka and Key and Retzius.

Many theories regarding the content of the ventricles have been considered since the overthrow of Galen's theory of the "animal spirit." It has at various periods been regarded as water, air, vacuum, vapor, until finally it was proved to be a fluid. Verduc, about 1700, insisted that fluid was never present in the normal ventricles, and this agitation led to Haller's vapor theory. Haller had the advantage of a correct knowledge of the circulation of the blood and supposed the vapor to be exhaled by the arteries and inhaled by the veins.

Cotugno (1770) first proved the existence of the subarachnoid space and in addition found fluid in this space in living fishes and turtles, but was unable to demonstrate fluid in dogs because the spinal cord so closely filled the dural envelope. Though he was the real discoverer of the existence of cerebrospinal fluid in the living animal, his findings were not accepted because of the firm belief in Haller's vapor theory. At this time all fluid was explained on the basis of some pathological process or as a post-mortem condensation of the vapor.

Galen's teaching that the pituitary body was the portal of exit of the ventricular contents was held by many until the end of the eighteenth century. Haller denied this function to the pituitary body, but Petit (1718) and even Monro (1793) supposed that hydrocephalus was due to sclerosis of the pituitary body, which effectually closed the channels of exit from the ventricles.

Monro (1793), after whom the foramen of Monro is named, was also interested in the study of hydrocephalus. The presence of a foramen (the foramen of Magendie), leading from the fourth ventricle to the subarachnoid space as claimed by Haller and Cotugno, was denied by many, including Monro. He said:

> The bottom of the fourth ventricle has no such communication with the cavity of the spinal marrow as Dr. Haller supposed, being completely shut off by its choroid plexus and pia mater. As further proof that the four ventricles communicate with each other and that they do not communicate with the cavity of the spinal marrow, I have observed in the bodies of every one of fifteen children who died from internal hydrocephalus that all the ventricles were distended; that on cutting into one of the lateral ventricles, all the ventricles were emptied, that in these cases, the passages above described were greatly enlarged, and that in none of them was water contained in the cavity of the spinal marrow or between its pia and the dura mater.

So near to the cause of hydrocephalus, in his zeal to prove a closed foramen, Monro, unfortunately, mistook it for the normal condition and left the discovery of the communication between the ventricles and the subarachnoid space to Magendie.

Without doubt, Magendie's contribution is the most important that has been made to the subject of hydrocephalus. He demonstrated by experiments on animals (1) that fluid normally fills the ventricles and the subarachnoid space; (2) that free communication exists between the ventricles and the subarachnoid space by means of a foramen which now bears his name; (3) that the central and spinal subarachnoid cavities form a single freely communicating space, and (4) that the aqueduct of Sylvius or the foramen of Magendie was obstructed in several cases of hydrocephalus.

Magendie, however, did not understand why hydrocephalus should result from an obstruction, for he thought the pia secreted the cerebrospinal fluid. He was led to believe that in some way the fluid could readily make its way upward through these membranous obstructions, but for some reason which he did not understand, its return was impeded and accumulation in the ventricles resulted.

The existence of cerebrospinal fluid has since been admitted, but the other observations of Magendie have been opposed. The controversy over Magendie's various claims and the views of more recent workers will be considered later.

3. INTERNAL HYDROCEPHALUS EXPERIMENTALLY PRODUCED

Flexner has noted that internal hydrocephalus sometimes follows the injection of the meningococcus into the subarachnoid space of monkeys. With this exception, we have been able to find no instance of hydrocephalus experimentally produced. The more common pathological processes producing internal hydrocephalus are usually so large (tumors) or so diffuse (inflammations) that it has been difficult to determine their exact part in the production of this disease. It is obvious that if hydrocephalus can be produced by experimental means, it will be possible to obtain definite information regarding its cause.

We conducted two series of experiments. In one, the aqueduct of Sylvius was occluded and in the other, the vein of Galen or the straight sinus or both were ligated. In each series the experiment was such that the function of either the aqueduct or of the vein was not disturbed.

I. EFFECT OF OCCLUSION OF THE AQUEDUCT OF SYLVIUS

In this series of experiments, in which an obstructing body was placed in the aqueduct of Sylvius, an internal hydrocephalus invariably resulted. It should be emphasized that the obstructing body was so placed *in* the aqueduct that the topographical relations were undisturbed and the lumen of the vein of Galen unaffected. The resulting hydrocephalus was therefore due solely to the mechanical occlusion of this channel. It is preferable to use a small obstructing body and depend on the formation of adhesions gradually to produce total occlusion. When this is done, practically no postoperative irritative effects result. A small pledget of cotton proved most efficient as the obstructing body.

These experiments were performed most successfully on dogs. Cats and monkeys were tried, but without success. When carefully done, the operative mortality in dogs was negligible. The animals at the time of operation were from 2 to 6 months of age. At this age the sutures of the skull are united so that the resulting hydrocephalus causes cerebral atrophy rather than enlargement of the head. Cerebral atrophy and cephalic enlargement are merely different expressions of the same underlying cause — increased intracranial pressure. Until the sutures are united, enlargement of the head is permitted by diastasis; after union the ventricular dilatation can be compensated only by cerebral atrophy and to a lesser degree by the displacement of external fluid and the absorption of bone.

The obstruction was placed in the aqueduct of Sylvius through a subcerebellar route as follows: Under ether anesthesia and strict surgical precautions, a bilateral, suboccipital decompression was made

through a posterior median incision. The defects in the bone and dura were made as large as possible to facilitate the subsequent procedure. The pia-arachnoid binding the cerebellum and the medulla was carefully cut on each side of the midline and an opening made corresponding to the foramen of Magendie, which is absent in the dog. The cerebellum and the roof of the fourth ventricle were raised by a small retractor. Through the artificial opening in the roof of the fourth ventricle a small pledget of cotton on the end of a graduated carrier was passed along the floor of the fourth ventricle into the aqueduct of Sylvius (Fig. 1). The pledget of cotton was deposited by withdrawal of

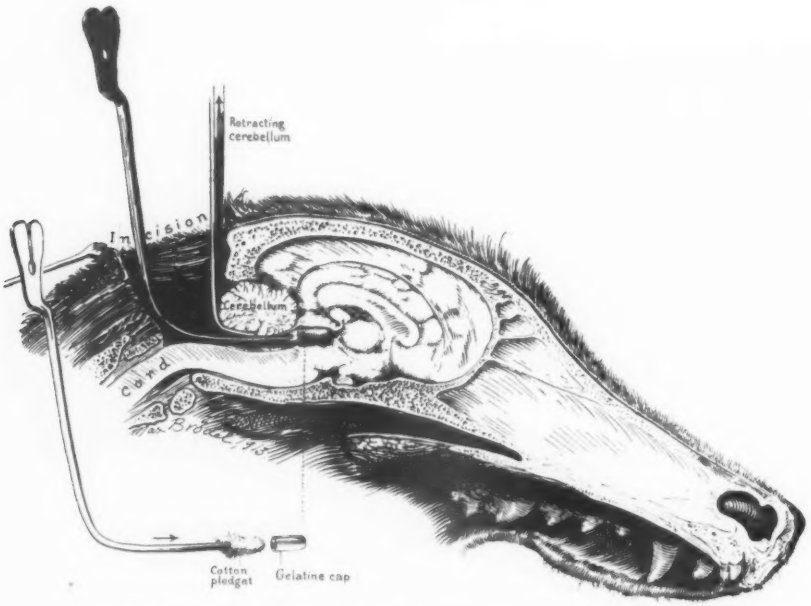

Fig. 1.—Midsagittal section of a dog's head to illustrate the method of procedure in the experimentl production of internal hydrocephalus. The obstruction is placed in the aqueduct of Sylvius by the subcerebellar route.

the carrier. A refinement of technic, though of doubtful benefit, consisted in enclosing the cotton in a gelatin capsule immersed in liquid petrolatum. The cerebrospinal fluid dissolves the capsule surrounding the cotton (Fig. 2). The introduction of the cotton was rendered easier when it was enclosed. This, however, was not essential and was of questionable value, as adhesions form less readily about the cotton.

With care, an accurate deposition of the obstructing body can be obtained. The anterior tip of the fourth ventricle can be determined from the reading on the graduated carrier. Often additional evidence was afforded by resistance to the carrier's progress. It is very easy to

deviate slightly and force the instrument into the mesencephalon, naturally with destructive results on account of the immediate proximity of the pyramidal tracts and the nuclei of the upper cranial nerves.

The recovery following operation was uneventful. Frequently a slight spasticity, disturbance of equilibrium and weakness of the extra-ocular muscles persisted for several days following the operation, but all soon disappeared. Vomiting and lethargy, general pressure signs were evident from the time of operation and these were the principal manifestations of internal hydrocephalus. Doubtless a bilateral choked disk would have been present and given the best evidence of the onset

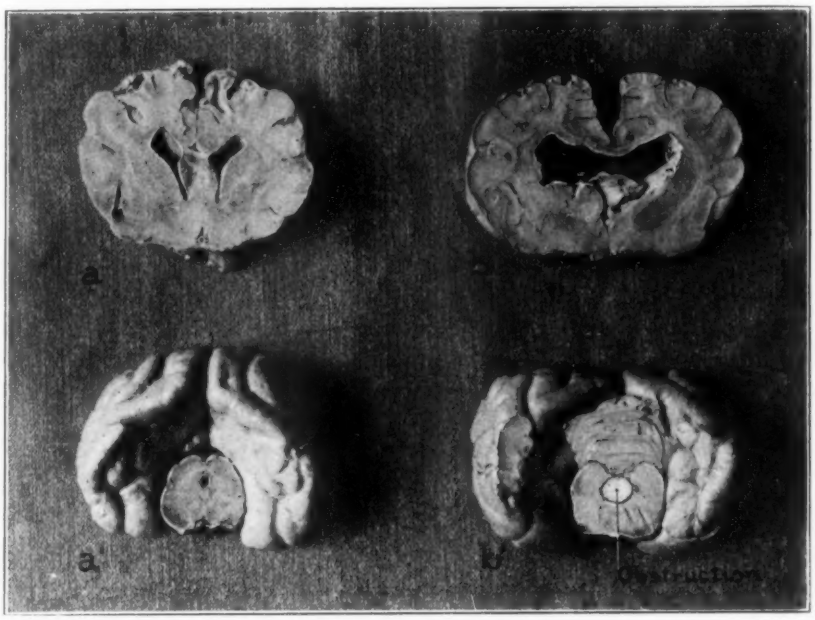

Fig. 2.—*a*, Cross-section of a normal brain of a dog at the level of the optic chiasm; *a'*, cross-section of the normal mid-brain of a dog to show the size of the aqueduct of Sylvius; *b*, cross-section of brain showing an experimental internal hydrocephalus of one month's duration; note the complete atrophy of the septum lucidum and fusion of the ventricles; *b'*, cross-section of the mid-brain of same animal showing the obstruction which had been placed in the aqueduct of Sylvius.

and progress of the intracranial pressure. Unfortunately, however, the eye-grounds were not examined. The animals were painlessly killed from three to eight weeks after operation. They were in good condition at the end of this time.

The citation of one experiment may be taken as representative of the entire group. Ether anesthesia was used in all experiments.

EXPERIMENT 1.—Jan. 9, 1911. Mongrel puppy, aged about 3 months; weight, 4½ pounds.

Operation.—A small piece of unencapsulated cotton was passed into the aqueduct of Sylvius by the subcerebellar route described above—no operative complications.

Postoperative History.—January 11: Marked loss of equilibrium with tendency to fall backward. Slight dissociation of ocular movements; slight spasticity but no paralyses; frequent vomiting; marked lethargy. January 17: General condition good. Equilibrium normal. Walks around slowly but no tendency to playfulness; spasticity has disappeared, ocular movements normal, vomiting persists. January 28: Lies curled up in the cage most of time; takes no interest in surroundings. Sluggishly responds to stimuli; tendency to stupor. Ocular movements normal; vomiting more frequent. Losing weight. February 9: *Killed by ether thirty days after operation.*

Pathological Note.—During the removal of the calvarium the forceps punctured a greatly thinned cortex and entered a large, distended lateral ventricle. The intraventricular pressure was so great that cerebrospinal fluid spurted a distance of three feet. The accompanying photograph (Fig. 2 *b.*) shows the obstruction in the aqueduct of Sylvius well organized and apparently impermeable. The third and lateral ventricles were greatly dilated and the thickness of the cortex was correspondingly diminished. Only an occasional shred of septum lucidum remained. The vein of Galen was normal.

II. OCCLUSION OF THE AQUEDUCT OF SYLVIUS FOLLOWED BY EXTIRPATION OF THE CHOROID PLEXUSES OF BOTH LATERAL VENTRICLES

Though we removed the choroid plexus from one or both lateral ventricles in a series of experiments, the bilateral removal was followed by the insertion of an obstruction in the aqueduct of Sylvius in only one experiment. The object of this experiment was to see if extirpation of the choroid plexus modified the development of the internal hydrocephalus. The operative procedure was as follows: A bilateral, subtemporal decompression was made. On each side the dura was opened and a transcortical incision was carried into the lateral ventricle at the junction of the body and the descending horn. By dilating the cerebral opening with a nasal dilator, a good exposure of the entire lateral ventricle was obtained and the choroid plexus almost completely extirpated. Despite the great vascularity of the choroid plexus, bleeding was slight and was readily controlled by cotton pledgets.

At the same operation a suboccipital decompression was performed and an obstruction passed along the subcerebellar or transventricular route and deposited in the aqueduct of Sylvius. The choroid plexus of the third ventricle and probably remnants of the choroid plexus of the lateral ventricles still remained in front of the obstruction. Prevention of fluid accumulation was possible only to a modified degree. There was lethargy and occasional vomiting.

Thirty-five days after the first operation, the suboccipital wound was reopened and found in perfect condition. The cerebellum was herniated through the osseous defect made at the previous operation.

This showed an increased intracranial pressure. A fine pair of forceps was passed along the floor of the fourth ventricle and the obstructing body readily located and grasped. It was firmly in position; there was beginning organization, and some force was required to dislodge it. On its release there was a gush of cerebrospinal fluid. An internal hydrocephalus had resulted from the occlusion placed in the aqueduct

Fig. 3.—Cross-section of a brain of a dog showing an internal hydrocephalus of five weeks' duration which resulted from obstructing the aqueduct of Sylvius. The choroid plexuses of the two lateral ventricles were simultaneously extirpated: *a*, at level of optic chiasm; note atrophy of septum lucidum and dilated lateral ventricles; *b*, to show the operative defect in the cortex; the dilated ventricles are closed only by the meninges; the remains of the septum lucidum are still evident; *c*, midbrain showing the obstruction in the aqueduct of Sylvius.

of Sylvius thirty-five days previously, *in spite of the almost complete bilateral extirpation of the choroid plexuses of the lateral ventricles.*

The obstructing body was replaced at once in the aqueduct, the animal killed and the brain hardened *in situ* with formaldehyd solution. Subsequent examination showed a completely occluded aqueduct. The pia had healed, covering the operative wound in the cortex. The hydrocephalus was distinctly modified, being much less than a hydrocephalus of the same duration, in which the choroid plexuses had not been removed. The difference is well shown by comparing the ventricles (Fig. 3) in this specimen with the ventricles in Figure 2. The obstruction in each was of practically the same duration, and in both the occlusion of the aqueduct was complete. The contrast is less striking, however, than it should be, because the brain of the former animal (Fig. 3) was hardened *in situ* and the ventricles more nearly resembled their actual size, whereas the brain in the latter (Fig. 2) was hardened after removal, and the opening of the ventricles, before fixation, resulted in considerable shrinkage. The inference is to be made that the extirpation of the choroid plexuses modifies the degree of the internal hydrocephalus.

The preceding experiments prove that *an internal hydrocephalus results from a simple mechanical occlusion of the aqueduct of Sylvius. From this it is apparent that cerebrospinal fluid forms in the ventricles, at least more rapidly than it is removed, and that the aqueduct of Sylvius is necessary for its escape.*

III. LIGATION OF THE VENA GALENA MAGNA AND THE SINUS RECTUS

That internal hydrocephalus may be due to an obstruction of the great vein of Galen or of the straight sinus has been suggested. In most of the pathological specimens used to support this theory, tumors have been present in the corpora quadrigemina, the pineal gland, the cerebellum or in this immediate neighborhood, and compression of the aqueduct of Sylvius in all probability has also resulted. The most conclusive clinical proof is given in a few recorded instances of a thrombosis of the great vein of Galen or straight sinus. Newman (1882) reported a case of hydrocephalus in which a small thrombus was present in the vena Galena magna at its junction with the sinus rectus. Browning also presented a case with a small thrombus in the sinus rectus.

Internal hydrocephalus resulting from venous obstruction is dependent on the venous collateral circulation. A good description of the venous collateral circulation of the veins of Galen is given in Poirier and Charpy's "Anatomy," 1901, iii, 60. This work is based largely on

that of Browning, Hedon and Trolard. The internal cerebral system of veins, of which the great vein of Galen is the trunk, is largely independent of the external venous system. It is not, however, a completely closed system. Collateral circulation is definitely established with the external system by the basilar, superior cerebellar, internal occipital, temporal, posterior corpus collosal and several smaller tributaries of the vena Galena magna. This is demonstrated by the fact that colored solutions injected into the straight sinus pass to the external system by these channels. Poirier and Charpy, however, minimize the importance of this collateral circulation and think it is

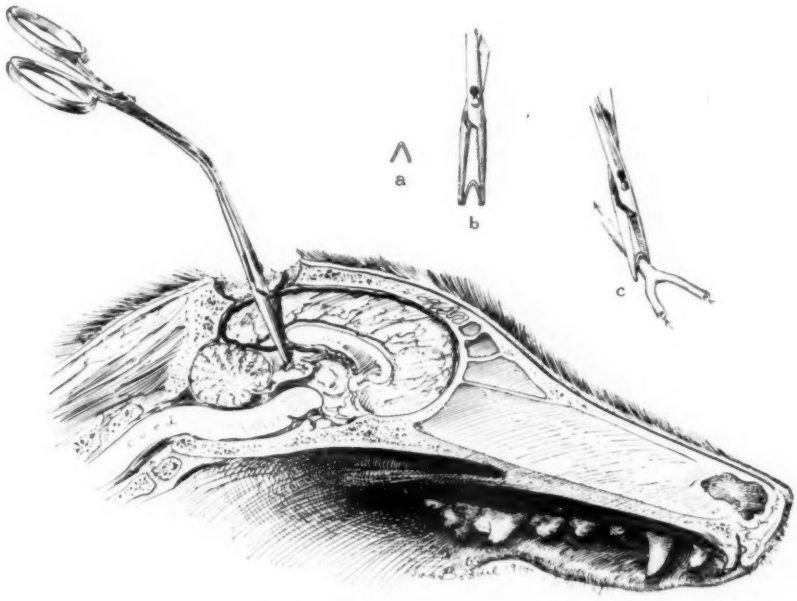

Fig. 4.—Drawing to indicate method of ligating the vena Galena magna. The silver clip is similar to that devised by Dr. Cushing. *a* shows the silver clip; *b*, in position in the clip holder, and *c*, its application on the vein.

insufficient to prevent internal hydrocephalus when the vein of Galen is obstructed. They further state that the small veins of Galen which drain practically the whole interior of the brain have almost no collateral circulation.

To determine the importance of venous obstruction in the production of internal hydrocephalus, we occluded the vein of Galen or the straight sinus or both in ten dogs. To do this a trephine opening was made just above the external occipital protuberance a little to either side of the midline. This opening was then enlarged with rongeur forceps. The dura was opened, reflected over the superior longitudinal

sinus and the occipital lobe separated from the falx cerebri. The straight sinus in the tentorium cerebelli (osseum) was traced downward to the vena Galena magna which is situated directly under the splenium of the corpus callosum. By careful blunt dissection the vein of Galen was isolated to permit the application of one or more silver clips (Fig. 4). These clips are similar to those designed by Dr. Cushing and act as most effective ligatures in wounds of such depth that ligation is impossible.

Fig. 5.—Internal hydrocephalus of three and one-half months' duration, produced by ligation of the vena Galena magna near its origin: *a*, dilated lateral ventricles, with atrophy of septum lucidum; *b*, to show the resultant dilated aqueduct of Sylvius; compare with normal Figure 2, *a'*.

In the ten dogs in which a ligation was thus accomplished, only one developed an internal hydrocephalus. In the other animals there was no evidence of ventricular enlargement.

Following the operation there was invariably an immediate recovery; in none were there any signs to indicate that the dogs were abnormal. All were as active and playful as the control animals. The

animals were under observation from one to eight months, and one gave birth to a litter of healthy puppies six months after the operation.

The single instance in which hydrocephalus resulted is of importance. The clip was placed just at the origin of the vena Galena magna, much lower than in any of the other experiments, thus barring the principal tributaries mentioned above from participation in the collateral circulation; the stasis resulting is no doubt similar to that in ascites which results from an obstruction to the vena cava, where the collateral circulation is insufficient to take over the additional work. The hydrocephalus was of three and one-half months' standing. The septum lucidum was largely destroyed, only shreds remaining. The ventricular dilatation was considerably less than in the dog in which the aqueduct of Sylvius was obstructed for thirty-five days and the choroid plexus of both lateral ventricles extirpated. The aqueduct of Sylvius was also larger than normal, showing the effects of its participation in the transmission of the increased ventricular fluid (Fig. 5).

In those dogs in which hydrocephalus did not develop, the clip was placed higher on the vein of Galen and nearer its junction with the sinus rectus. When the clip was so placed, or when the straight sinus alone was ligated, there was no evidence of fluid stasis and the ventricles remained normal in size, showing that below this point there was sufficient venous collateral circulation to prevent the formation of hydrocephalus.

It is therefore evident that a low obstruction of the vena Galena magna may result in the production of an internal hydrocephalus, but that a high ligation has no such effect.

4. THE FORMATION OF CEREBROSPINAL FLUID

I. THE EXISTENCE OF CEREBROSPINAL FLUID

Since the introduction of lumbar puncture by Quincke (1891), the existence of cerebrospinal fluid can be demonstrated at any time. That fluid rapidly reforms after withdrawal either from the ventricles or the subarachnoid space can also be demonstrated. Following ventricular puncture in hydrocephalus or after lumbar puncture in cerebral tumor with a postoperative cerebral hernia, the rapidity of the formation of fluid can be estimated. In either case the tension prior to the puncture is reestablished within a few hours, showing that the fluid removed by puncture has reformed during this time. The rapidity of formation can be observed in the rare condition known as rhinorrhea, in which the cerebrospinal fluid discharge may be 200 c.c. or even more in twenty-four hours.

The problem of the formation of cerebrospinal fluid concerns both the place and the manner of its formation.

II. THE PLACE OF FORMATION OF CEREBROSPINAL FLUID

Magendie thought cerebrospinal fluid was formed from the pia, saying:

> The pia is almost exclusively a tissue of blood-vessels, and resembling very closely the pulmonary parenchyma, offers the most favorable conditions for a secretion, prompt and considerable. Everything, therefore, leads us to suppose the pia to be the secretory organ of the cerebrospinal fluid.

Magendie tried some injection experiments which tended to confirm this opinion, though he realized the necessity of further proof of a more direct character. He also realized the difficulty of harmonizing this view with his anatomical observations in hydrocephalus.

Lewandowsky was of the opinion that cerebrospinal fluid was a brain product and that only a small part of it could be ascribed to transudation from the choroid plexuses. Spina concurred with this view, but thought the cerebrospinal fluid was a product of transudation not only of the capillaries in the brain, but also in the pia mater. Schmorl noted serological differences in the cerebrospinal fluid of the ventricles and the subarachnoid space and concluded that fluid was formed both in the ventricles and in the pia. He further asserted that no communication existed between the ventricles and the subarachnoid space. Kafka, in a series of eighteen cases, was unable to verify these differences in serological (mainly Wassermann) tests.

The experiments concerning the production of internal hydrocephalus show that fluid forms in the ventricles. This is substantiated in hydrocephalus, in which there is obstruction to the outlets from the ventricles. The experiment in which a modified grade of hydrocephalus followed the total occlusion of the aqueduct of Sylvius and the bilateral extirpation of the major part of the choroid plexuses of the lateral ventricles is evidence of a direct character that the choroid plexuses, as has been suggested, are the organs from which this fluid is produced.

We do not maintain, however, that all cerebrospinal fluid is formed in the ventricles or from the choroid plexuses. Since transudation is partly responsible for this fluid formation, it is possible that fluid might be formed externally in the subarachnoid space, as has been suggested by Schmorl. Evidence for the extracerebral formation of cerebrospinal fluid is found in internal hydrocephalus, in which the foramina of Luschka and Magendie are occluded and all the choroid plexuses are enclosed in the ventricles. In such conditions though cerebrospinal fluid may be obtained by lumbar puncture it is always very small in amount and reforms very slowly. In Case 4, Group 1 (N. M.), never more than 3 c.c. were obtained, and frequently lumbar puncture yielded no fluid. In Case 5 of Group 1 (M. R.), all the

choroid plexuses were enclosed in the cerebral ventricles and the clinical and pathological observations showed an absence of communication between the ventricles and the subarachnoid space. By lumbar puncture, however, 5 c.c. of spinal fluid could be obtained. The ventricular and spinal fluids differed but little in composition. The amount of reducing substance (Fehling) was equal in the two. Hexamethylenamin, given by mouth, appeared in each in the same minute quantity, and the cell-count of the two fluids was the same. The choroid plexuses of this patient could obviously play no *direct* part in the formation of the fluid in the subarachnoid space. This fluid, small in amount, which reformed only after several hours, could be derived from one of two sources, either as a transudate from the pial vessels or as a transudate through the thin wall of the dilated fourth ventricle.

In Case 7, Group 1 (M. N.) the spinal and ventricular fluids were of similar composition, and an absence of communication between the ventricles and the subarachnoid space was clinically demonstrated. Twelve hours after a ventricular injection of phenolsulphonephthalein a minute trace of this color was present in the spinal fluid.

Since phenolsulphonephthalein, when present in concentration in the blood, does not appear in the cerebrospinal fluid, it is probable that the trace in the spinal fluid of this patient also was derived by transudation from the ventricles. The foregoing data are, however, insufficient to permit us to assert that the spinal fluid is formed in such a manner.

Although the choroid plexuses were known to Herophilus of Alexandria, Galen gave them the name by which they are known at the present day. Various functions have been ascribed to these structures. Willis (1664) thought they were blood-filters; Varoli, that they sucked up the ventricular fluid; Riolanus noted their exceptional vascularity and called them *rete morabile;* Nuck (1696) first believed them to be glands, a view which was soon received with favor, though various fanciful suggestions regarding them have been expressed since. Ruysch (1700) modified this general glandular conception to that of a cerebrospinal fluid-forming gland. Purkyne (1836) noted the epithelial character of their lining cells, but did not draw any conclusions concerning their function. Special attention was attracted to the secretory nature of this epithelium by Faivre (1854) and Luschka (1855).

Even at the present day there is no agreement of opinion as to the manner of production of cerebrospinal fluid.

One group favors the view that cerebrospinal fluid, like other body fluids, is produced by simple filtration through an animal membrane and that their differences depend on osmotic pressure between the capillaries and the serous spaces. This view is supported by Leonard Hill, Starling and Mestrezat. Another group, influenced by Heiden-

hain, chiefly, explains the formation of fluids on the basis of a cellular activity, or an active rather than a passive formation. In favor of this view are Galeotti, Cappellati, Cavazzani, Studnicka, Goldman, Schläpfer, Kingsbury, Mott and others.

1. The Manner of Formation, Based on the Composition of Cerebrospinal Fluid

Schmidt (1850) was the first to demonstrate differences between the composition of the cerebrospinal fluid and other serous fluids and between the blood-plasma and the cerebrospinal fluid. On this basis he suggested a secretory process of formation for cerebrospinal fluid. That which principally differentiates this fluid from other body fluids is its very low solid content and consequently its low protein content. The total solids are about one-seventh or one-eighth and the protein content about one three-hundredths of the blood-plasma content. This difference is most marked between the cerebrospinal fluid and the blood-plasma, but also obtains between the cerebrospinal fluid and the pericardial, peritoneal and other serous fluids. The specific gravity of the cerebrospinal fluid is 1.003, as compared to 1.028 for the blood-plasma. It is difficult, indeed, to understand how differences of osmotic pressure alone, acting on a common fluid medium and through the same vascular endothelium, could produce such differences as exist in the chemical composition of the various fluids.

As further evidence of the secretory theory of formation, it has been pointed out that the composition of cerebrospinal fluid resembles saliva more closely than it does the other serous fluids; while the salt content of saliva is somewhat higher, the water, total solids, protein content and specific gravity in cerebrospinal fluid are very similar. For some time a reducing body—pyrocatechin of Halliburton—was regarded as specific for cerebrospinal fluid. Halliburton has since shown this reducing substance to be glucose. Nawratzki confirmed the presence of sugar and estimated that it was present in about the same amount as in the blood. Cavazzani noted a minimum alkalinity of the cerebrospinal fluid as contrasted to the blood. He also declared that he had found a diastatic ferment, but Panzer and Lewandowsky were not able to confirm this finding. Kafka noted a lipolytic ferment. Other differences of a specific character have been reported, but most have been disputed, so that they are not now available as evidence of secretory activity.

Against the secretory theory of formation of cerebrospinal fluid is the mineral content of cerebrospinal fluid. Halliburton, Schmidt and Nawratzi determined that it was essentially the same as that of the parent blood-plasma and the other serous fluids. Simple filtration would seem to explain best this similarity of salt content.

2. *The Manner of Formation Based on the Anatomy and Histology of the Choroid Plexus*

The choroid plexuses are unique specialized structures, placed in every ventricle. That they are endowed with an exceptional blood-supply and covered by cells of a special character would seem to indicate that they are structures with a special function.

The elaborate blood-supply might well appear to indicate a filter-bed, while the specialized epithelium would indicate a gland. It would seem that there could be little doubt, from an anatomical point of view alone, that by one or both of these methods cerebrospinal fluid is supplied to the ventricles from the choroid plexuses. As noted above, Faivre and Luscka first emphasized the character of the epithelium and from analogy insisted on its secretory character. Their views have since been strengthened by the histological observations of Petit and Girard, Meek, Galeotti, Schläpfer, Goldmann, Immamura, Voshimura, Hworostuchin, Francini and others. The choroidal epithelial cells are large, cubical and often columnar, with a granular cytoplasm and basal nuclei. The cells are similar in appearance to gland cells, and such a histological picture is hardly conceivable without a secretory activity.

In addition to the general glandular appearance, granules, presumably of a secretory character, have been observed, both post-mortem and by intra-vitam staining methods. Galeotti (1897) first noted basophil and acidophil granules. These findings were substantiated by Bibergeil and Levaditi, Francini, Schläpfer and Goldmann, principally by the use of intra-vitam staining methods. Hworostuchin observed mitochondria, which he thought indicated the secretory activity of the plexuses. In addition, he noted the presence of nerves in the choroid plexus.

3. *The Manner of Formation Based on the Action of Drugs on the Rate of Production of Cerebrospinal Fluid*

It has been suggested that cerebrospinal fluid is formed by the secretory activity of the epithelium of the choroid plexus, because after the administration of drugs which stimulate glandular secretion there is supposed to be an increased production of cerebrospinal fluid and the cells show a histological change similar to the discharged appearance of the cells of the salivary glands. Petit and Girard, and Meek observed a swollen appearance of the choroid epithelium, a peripheral cytoplasmic clear zone and often cellular rupture following the administration of pilocarpin; Capelleti, Cavazzani and Petit and Girard obtained after the injection of pilocarpin an increased flow of cerebrospinal fluid from a subarachnoid fistula and compared this with

the effect on the salivary glands. They also noted an increase following ether, amyl nitrite and a diminished flow following atropin and hyoscyamin. Sicard was unable to confirm this. Dixon and Halliburton recently considered this subject in detail. They found only a slight increase of cerebrospinal fluid following injection of pilocarpin, atropin, amyl nitrite and various salts; and a definite increase following ether, chloral hydrate, chloroform, choroid plexus extract and brain extract.

In order that conclusions of value may be drawn from experiments of this nature, several precautions are necessary. The anesthetic must be constant and the animal must be sufficiently anesthetized to insure perfect quiet throughout the experiment. Vapor anesthetics cause great variations in the rate of flow of the fluid, and change of respiration produces similar results. To minimize these influences we used chlorbutanol, administered by stomach-tube; with this drug a very even anesthesia was secured. Rather than insert a cannula at random into the subarachnoid space, we exposed and trephined the atlas, and opened the dura by a stellate incision. Into the trephine opening in the atlas a special fitting cannula was inserted. The animal was then placed in a sling in such a manner that the cannula was at the most dependent part, and the fluid from both the head and the spinal canal ran into this as into a funnel. By this technic, bloody fluid was not obtained, and fluid did not accumulate as occurs when a needle is inserted through the dura. Clogging of the cannula does not occur and the experiments may be continued for several hours. To insure a steady outflow of cerebrospinal fluid we waited from fifteen to twenty minutes, or until the accumulated fluid had escaped. Drops were counted over arbitrary periods of five minutes. The results of these observations are represented in the accompanying charts (Fig. 6).

The most striking and uniform result obtained in these experiments followed the temporary compression of the jugular veins. Except in one instance there was always a marked and instantaneous increase of cerebrospinal fluid following jugular compression. We believe this can be explained only by an increased production of fluid. It is conceivable that it might be due to displacement of fluid by the cerebral congestion. If this were so, a retarded flow would be expected after the restoration of the equilibrium in the blood-vessels, but in each instance the previous level of fluid escape was reestablished. Moreover, the same results were obtained following jugular compressions frequently repeated at short intervals. When pressure on the jugular veins was maintained for a longer period of time, the increased flow did not continue, but gradually returned to normal. This was due, no doubt, to rapid establishment of collateral venous circulation.

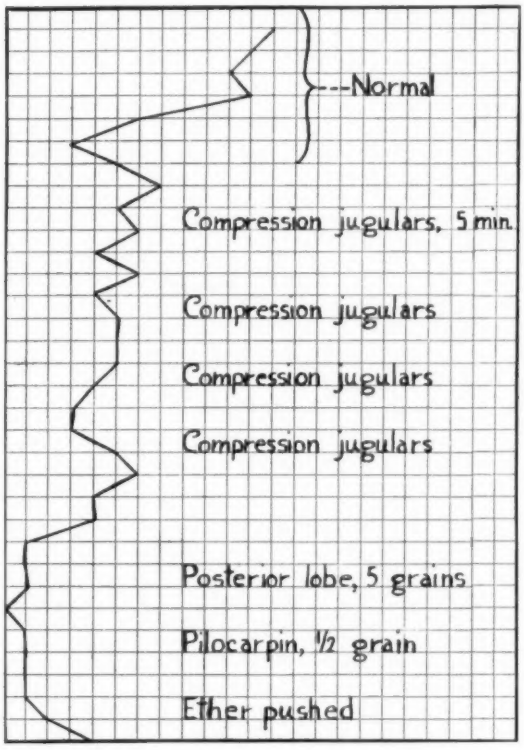

Figure 6 A.

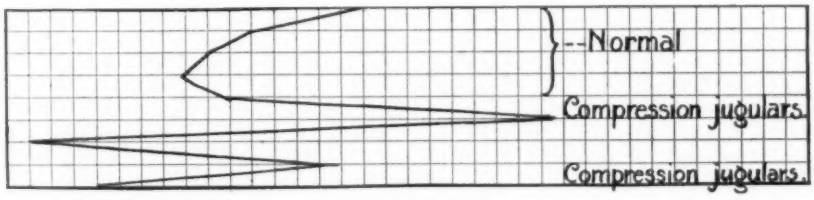

Figure 6 B.

Fig. 6.—Curves representing actual flow of cerebrospinal fluid from subarachnoid fistula, as influenced by drugs and mechanical factors. The base line represents time, each division being a five-minute interval. The vertical line represents the actual number of drops in each five-minute interval. The drugs used are entered during the progress of the curves.

(The remainder of these curves are shown on succeeding pages).

Since general cerebral venous stasis (jugular compression) results in increased cerebrospinal fluid formation, the place of formation of this fluid is probably from the vessels on the surface of the brain as well as in the ventricles. Owing to the efficient collateral on the surface of the brain, the formation of the fluid there is but transient, whereas in obstruction to the vein of Galen (low ligation and poor collateral) the increased production in the ventricles is continuous.

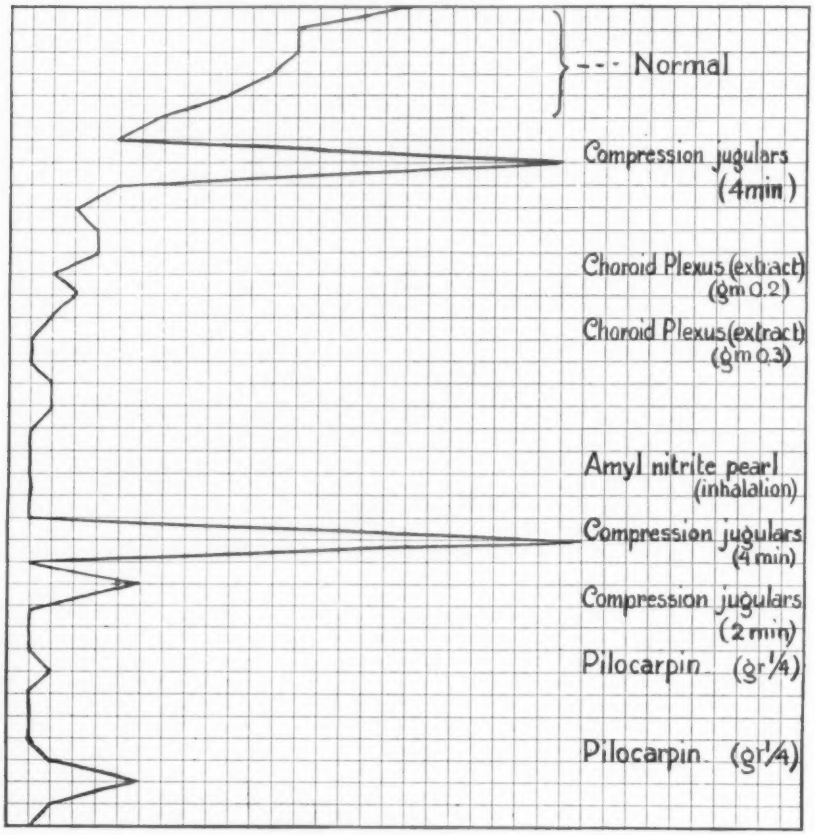

Figure 6 C.

In a number of experiments ether caused an increased production of fluid. It is probable that this increase is also due to venous stasis. The effect is not continuous, but occurs regularly with each application of ether. Amyl nitrite caused no such increase of fluid. The effect of pilocarpin on the increase of fluid production is slight, but always positive. When compared to the secretion which results from the stimulation of the salivary glands, however, it is practically negli-

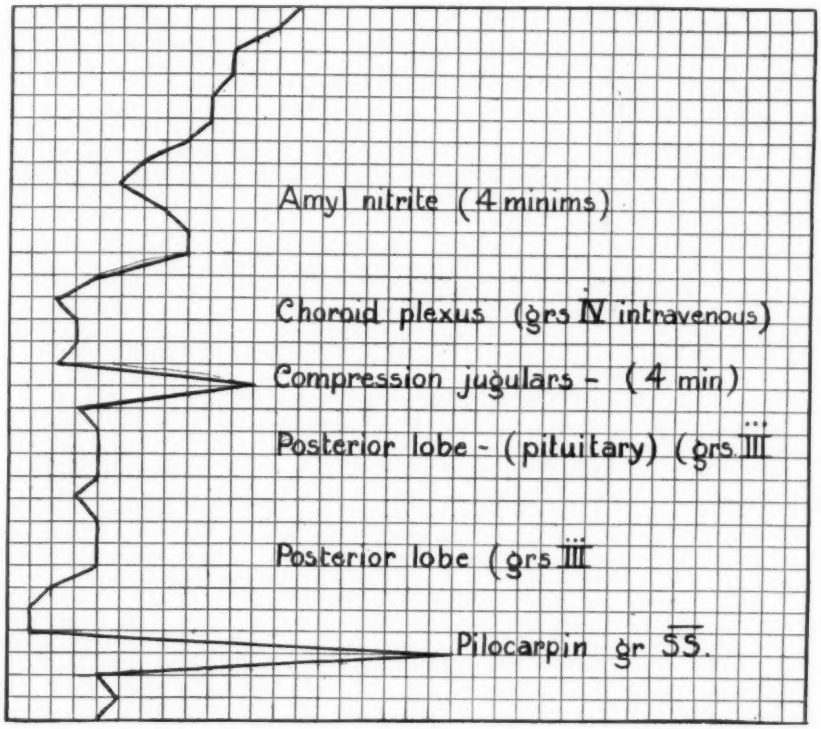
Amyl nitrite (4 minims)
Choroid plexus (grs IV intravenous)
Compression jugulars - (4 min)
Posterior lobe - (pituitary) (grs III)
Posterior lobe (grs III)
Pilocarpin gr SS.

Figure 6 D.

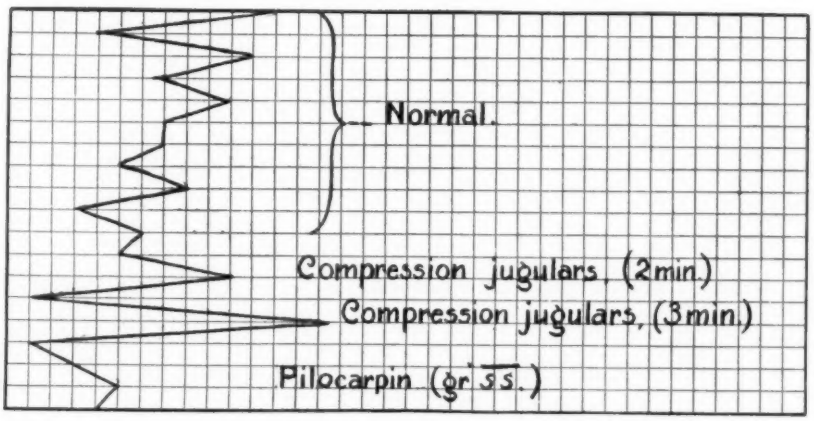

Figure 6 E.

gible. An animal when given pilocarpin will drown in its own salivary secretion, but the cerebrospinal fluid outflow increases only a few drops. We hesitate to make any positive deductions of glandular activity on such small though fairly constant results. Though no mechanical factors which might cause congestion and thereby filtration were noted during these experiments, this possibility must be borne in mind.

Repeated intravenous injections of freshly prepared aqueous extracts of choroid plexus and of posterior lobe of the pituitary body of the ox or sheep failed to produce an increased rate of flow of cerebrospinal fluid. This is contrary to the results of Dixon and Halliburton. They obtained a definite increase after the injection of extract of choroid plexus.

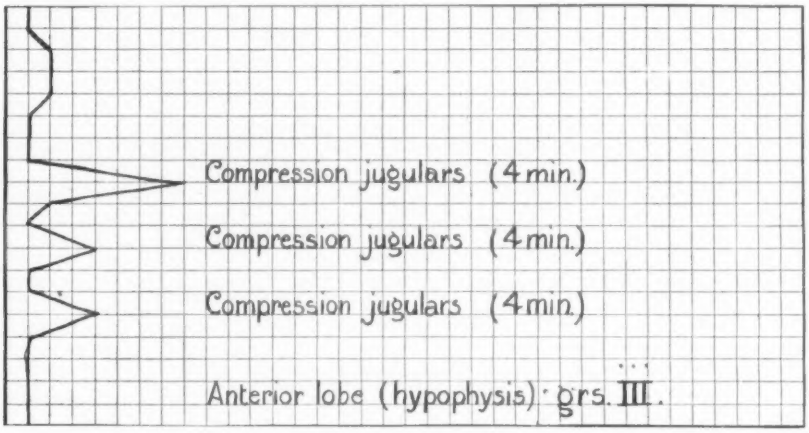

Figure 6 F.

Following the experiments with pilocarpin the choroid plexuses were removed for microscopic examination. We were unable to find definite histological alteration in the structure of the gland. Frequently, ruptured cells were observed, but these are often seen in the normal choroid plexus. From a purely objective point of view, it was impossible to tell from the choroid plexus whether or not a previous injection of pilocarpin had been made.

4. The Manner of Formation Based on the Impermeability of the Choroid Plexus

One of the strongest arguments in favor of the secretory theory of cerebrospinal fluid formation is the difficulty with which foreign substances pass from the blood to the cerebrospinal fluid. Were it entirely a simple mechanical process of filtration, it is difficult to under-

stand why simple substances should not readily pass through into the cerebrospinal fluid. It has been observed frequently that when very large doses of potassium iodid are administered, none passes into the cerebrospinal fluid. It has also been noted that in obstructive jaundice, bile pigments cannot be demonstrated in the cerebrospinal fluid. It is evident that a mechanism which can prevent the passage of certain substances into the cerebrospinal fluid must play a very important rôle in the prevention of the hematogenous transmission of infections to the central nervous system, and, for the same reason, when affections of the central nervous system exist, they are correspondingly refractory to remedies conveyed by the blood.

Such an impermeability to the cerebrospinal fluid has been shown to exist for numerous substances. Sicard was unable to obtain methylene-blue or potassium iodid in the cerebrospinal fluid when large doses were given subcutaneously, intravenously or by mouth. Rotky was unable to detect iodids, bromids, salicylates, mercury or bile pigments. These observations have been extended to include serological investigations. Widal and Sicard could not demonstrate agglutinins or immune bodies in the cerebrospinal fluid in typhoid fever. The behavior of the Wassermann reaction in the cerebrospinal fluid of hereditary syphilis without involvement of the central nervous system gives further evidence of the impermeability of the choroid plexus to foreign substances. In the majority of patients[1] whom we examined, the reaction was positive in the blood, but in no instance was there a positive reaction in the cerebrospinal fluid.

This impermeability, however, is not absolute; traces of many substances have been found in the cerebrospinal fluid. In certain diseases affecting the central nervous system there is a permeability. Sicard, Rotky, Capka and Mott showed this in meningitis, diabetes and uremia. Achard and Ribot observed traces of potassium iodid, Lewin and Bernard traces of salicylates, and Sicard traces of mercury in chronic mercurial poisoning, Olmer and Tian, Castaigne and others noted bile pigments in jaundice. Crowe noted hexamethylenamin, Rotky uranin and Lewandowsky strychnin. Zaloziecki observed immune bodies and agglutinins in typhoid fever, and thought that their quantity was dependent on the albumin content of the cerebrospinal fluid and the high concentration of immune bodies in the blood. We determined the presence or absence in the cerebrospinal fluid, of various substances after ingestion, and intravenous and subcutaneous administration. These observations were made on animals and in patients from the hospital wards. The results are given in Table 1.

1. These were patients from the Pediatric Clinic and the observations have not been published.

TABLE 1.—EXPERIMENTS TO DETERMINE THE PRESENCE OR ABSENCE OF VARIOUS SUBSTANCES IN THE CEREBROSPINAL FLUID AFTER ORAL, INTRAVENOUS AND SUBCUTANEOUS ADMINISTRATION

I. ANIMAL TESTS

Substance used	Amount	How given	Time of test after administration	Test in C. S. F.*	Other fluids
Methylene blue	30 c.c.	Intravenous	45 min.	—	Aqueous humor negative.
Indigocarmin	60 c.c.	Intravenous	30 min.	—	Peritoneal and pericardial positive; aqueous humor negative.
Phenolsulphonephthalein	100 mg.	Subcutaneous	90 min.	—	Pericardial and aqueous humor negative.
Potassium iodid	30 gr.	Subcutaneous	60 min.	—	
Potassium iodid	60 gr.	Mouth	4 hrs.	—	None in aqueous humor.
Potassium iodid	50 gr.	Intravenous	30 min.	—	Pericardial fluid negative.
Strychnin	¼ gr.	Subcutaneous	15 min.	--	
Morphin..	½ gr.	Subcutaneous	30 min.	--	
Trypan blue	1 gm.	Intravenous	60 min.	—	
Hexamethylamin	45 gr.	Mouth	60 min.	+	Pericardial pleural fluids and aqueous humor positive.

II. CLINICAL TESTS

Hexamethylamin	10 gr.	Mouth	2 hrs.	+	
Bile pigments	Obstruction 2 months	.....	2 mos.	—	
Bile pigments	Catarrhal jaundice 3 weeks	.....	3 wks.	—	
Bile pigments	Obstruction 3 weeks	.....	3 wks.	+	
Sodium salicylate	30 gr.	Mouth	60 min.	+	
Potassium iodid	40 gr.	Mouth	40 min.	—	

*In this column + means positive and — negative.

These results confirm those of many previous investigators. Of the various substances used, only hexamethylenamin and sodium salicylate were detected in the cerebrospinal fluid. The test for these substances is very delicate, and this may explain their detection in the cerebrospinal fluid. It is worthy of note that in dogs sodium salicylate and hexamethylenamin were obtained, in traces, in the vitreous humor. In several of the animal tests the aqueous humor was examined and the findings were almost identical with those of the cerebrospinal fluid.

It is striking that in spite of the actual flooding of the blood with colored solutions, such as phenolsulphonephthalein, indigocarmin, trypan blue and bile pigments, not even traces are present in the cerebrospinal fluid. In our experiments the animals were deeply colored following intra-vitam staining with trypan blue, and even the choroid plexuses were deeply stained, but the cerebrospinal fluid remained colorless—an observation frequently made by Goldmann. Indigocarmin *was found in both the peritoneal and the pericardial fluids,* but *not* in the cerebrospinal fluid or in the aqueous humor.

From these observations it would appear certain that the passage of substances into the normal cerebrospinal fluid is very difficult, and that when it occurs they appear only in faint traces. It is also apparent that there is greater difficulty in the passage of substances into the cerebrospinal fluid than into the other serous fluids. It seems difficult to attribute this fact to mechanical inhibition alone, but rather to a selective or discriminating cellular activity.[2]

IV. SUMMARY OF THE FORMATION OF CEREBROSPINAL FLUID

It can be definitely stated that cerebrospinal fluid forms in the ventricles. From evidence partly direct, but more largely indirect, there can be but little doubt that the choroid plexuses (possibly including the ependyma) produce this fluid. Whether this formation is alone by secretory or mechanical means or by both is impossible to say absolutely from the evidence at hand. Certainly fluid is readily and rapidly formed by the induction of venous stasis, and when the collateral circulation is insufficient (as the small veins of Galen and the beginning of the large vein of Galen), the increased production may be continuous and hydrocephalus result. How far the normal

2. Ducrot makes an interesting observation which, if substantiated, is indicative of therapeutic possibilities. He asserts that injections of methyl violet are followed by the appearance of the contents of the blood-plasma in the cerebrospinal fluid and in the proportions found in the blood. In jaundice, bile also readily passes into the cerebrospinal fluid following methyl violet injection. His explanation is that methyl violet paralyzes the secretory choroidal epithelium and the result is a temporarily inactive membrane. Filtration is then inhibited. This he also uses as proof of the secretory formation of cerebrospinal fluid. After several hours the effects of this drug wear away and the normal action of the choroid plexus is again restored.

differences of intravascular pressure cause transudation or production of cerebrospinal fluid cannot, however, be inferred by the production of artificial pressures. The similarity of the saline content of the blood and cerebrospinal fluid would seem to be undoubted evidence that filtration must be partially responsible for this fluid production

On the other hand, the histological character of the choroid plexus epithelium, the radical difference in the chemical composition of the cerebrospinal fluid in comparison to the blood and other serous fluids and the protection of the cerebrospinal fluid from substances in the blood (impermeability) necessitate the assumption of a cellular or secretory activity. It therefore seems most probable that cerebrospinal fluid is formed both by filtration and by secretion.

5. ABSORPTION OF CEREBROSPINAL FLUID

The maintenance of a proper amount of cerebrospinal fluid in the ventricles and the subarachnoid space requires that there shall be an absorption equal to the formation. The first proof of an active circulation of cerebrospinal fluid was obtained by the experiments of Magendie. He demonstrated, after draining the subarachnoid space of as much fluid as possible, that there was such an active reformation that an equal amount of fluid could be again obtained on the following day or even sooner. He also demonstrated an active absorption of colored solutions when they were injected into the subarachnoid space and noted their presence in the jugular veins and in the urine.

Long before this absolute evidence, an active discharge of the ventricular content, whether fluid, vapor or animal spirits, had been presumed. As previously mentioned, Galen believed that the discharge of the material resulting from the purification of his animal spirits took place through the infundibulum and cribriform plate into the nose, where it was recognized as "pituita." Though Galen's theories of the animal spirits were attacked by Vesalius (1543) and later overthrown, his view that the infundibulum was the portal of exit for the ventricular content was accepted by many even until the time of Magendie (1825).

I. HISTORY

Lymphatics in the dura were described by Mascagni about 1775. Meckel (1777) supported this observation and referred to them as "vasa resortentia lymphatica." Arnold (1838) asserted the presence of lymphatics in the pia-arachnoid membranes and ascribed absorption of the cerebrospinal fluid to them. His (1850) and von Recklinghausen (1863) agreed with this observation and also noted the presence of perivascular lymphatics.

Böhme (1869) asserted the existence of a unique, independent system of valveless lymphatics which directly connected the subarachnoid

space with the pial vessels, forming in reality an accessory system to the blood-vessels. He maintained that there were large stomata which allowed free access to these vessels from the subarachnoid space. During congestion these vessels filled with blood, but despite the unguarded openings the blood did not pass into the cerebrospinal fluid. Milk and granular substances injected into the subarachnoid space, however, passed readily over into the veins through these stomata and the intermediary system of lymphatics. These stomata, demonstrable by silver nitrate staining, were similar to the diaphragmatic stomata, advocated only a short time before by von Recklinghausen.

Key and Retzius (1875) attributed the absorption of cerebrospinal fluid to the pacchionian granulations. During the injection of colored solutions under pressure into the subarachnoid space, they were able to observe such solutions passing through the pacchionian bodies into the longitudinal sinus.

II. METHODS OF TECHNIC

Though many investigations have been conducted to determine the method of exit of the cerebrospinal fluid, the results have been variable and inconclusive. They have been inconclusive chiefly because the experimenters have used artificial pressures, or the injections have been made post mortem. In all experiments here submitted the conditions have been as near normal as possible; no pressure was used, and the animals were alive (ether anesthesia). The results of the experiments represent as nearly as can be determined the natural processes of absorption.

The principal method used in solving this problem was by substituting inert colored fluids for an equal amount of cerebrospinal fluid and then determining the quantitative output of these substances in the urine. The substance must necessarily be one that is readily absorbed and quickly eliminated by the kidney.

We tried indigocarmin, methylene-blue and phenolsulphonephthalein. Methylene-blue and indigo-carmin were of little value in these experiments, so almost sole reliance was placed on phenolsulphonephthalein. Methylene-blue was but slowly excreted and appeared in the urine as a leuko-body, which rendered its quantitative estimation uncertain. Indigocarmin appeared more rapidly in the urine, but its color was affected by urinary pigments to such an extent that even an approximate quantitative value could not be estimated. Phenolsulphonephthalein met all requirements. The question of the excretion of phenolsulphonephthalein by the kidney has been investigated thoroughly by Rowntree and Geraghty, who introduced it as a test of the renal function. By virtue of its stability, its inert character, its rapid,

uniform and almost complete elimination by the kidney, its easy and accurate quantitative estimation, phenolsulphonephthalein is well adapted for this study. It has been used recently by Dandy and Rowntree in the estimation of absorption of fluids from the pleural and peritoneal cavities.

On account of the difficulty and uncertainty of performing lumbar punctures on dogs, owing to the great length of the cord, we obtained the cerebrospinal fluid from the cisterna magna. After exposing the occipito-atlantal membrane it was possible to puncture the transparent arachnoid membrane and siphon off the desired amount of fluid. The fluid was replaced by an equal amount of phenolsulphonephthalein solution at body temperature. One c.c. (6 mg.) of phenolsulphonephthalein was chosen as the amount for injection in these experiments. In each instance the time of the appearance of the substance in the urine and the quantitative output in the urine over periods of one and two hours were determined. The quantity excreted in the urine was determined by colorimetric readings in Rowntree and Geraghty's modification of the Autenrieth-Königsberger colorimeter.

It should be emphasized that these percentages should not be taken as absolute, for the total amount of phenolsulphonephthalein injected cannot be recovered in the urine. In the peritoneal and pleural cavities one can recover from 80 to 90 per cent., but, for some reason which is not evident, only 60 to 90 per cent. can be recovered after injection into the subarachnoid space. The results are sufficiently accurate for all practical purposes. The accompanying figures represent the percentage recovered of the amount injected.

III. THE RATE OF ABSORPTION OF CEREBROSPINAL FLUID IN DOGS

The following experiment is characteristic of the series:

EXPERIMENT 2.—May 26, 1911. Female dog, weight, 14½ pounds. One c.c. (or 6 mg.) of phenolsulphonephthalein substituted for 1 c.c. of cerebrospinal fluid (ether anesthesia). Time of injection, 10:02 a. m. Time of first appearance in urine, 10:07 a. m., five minutes. The hourly output is given in Table 2.

TABLE 2.—PHENOLSULPHONEPHTHALEIN EXCRETION IN EXPERIMENT 2.

Hours After Injection.	Time	Output of Phenolsulphonephthalein. Per Cent.
1	11:07 a. m.	16.6
2	12:07 a. m.	17.8
3	1:07 p. m.	13.6
4	2:07 p. m.	7.2
5	3:07 p. m.	4.5
6	4:07 p. m.	2.2
7	5:07 p. m.	1.3
8	6:07 p. m.	.3
9	7:07 p. m.	+
Total amount excreted in 9 hours		63.5

Five days later another injection on the same animal gave identical results.

We can conclude that there is an active circulation of cerebrospinal fluid. For a period of from three to four hours the absorption is fairly regular and after this time progressively diminishes. This diminution is in all probability due to the dilution by the fluid which is being constantly formed. It may be said that the cerebrospinal fluid is completely absorbed and renewed at least every four or six hours, or at least from four to six times every twenty-four hours. Experiments in which methylene-blue and indigocarmin were used were similar in time of appearance and disappearance, though a quantitative value could not be obtained.

The quantitative results of absorption from the human subarachnoid space are similar to these results in animals.

IV. DOES ABSORPTION OF CEREBROSPINAL FLUID TAKE PLACE INTO THE BLOOD OR INTO THE LYMPH?

There are two ways by which absorption of cerebrospinal fluid could occur—the blood and the lymph. Mott, who is the strongest exponent of the theory of lymphatic absorption, thinks perivascular lymphatics perform this function. The prevalent view, however, is that, with the possible exception of lymphatic connections along the olfactory and optic nerves, the central nervous system, including the meninges, is destitute of lymphatics. The present conception of the lymphatic system is that it is everywhere closed by endothelial cells, and that all its branches converge either to the thoracic or to the right lymphatic duct. Except for the work of Key and Retzius, who believe that the filling of the lymphatics occurs along the nerve sheaths, we know of no evidence of lymphatic absorption. Their experimental injections, however, were made under high pressure and were performed post mortem. Evidence of this character is open to the most severe criticism. Normally the cerebrospinal fluid does not pass along the sheaths of the nerves with exception of the olfactory and optic nerves.

Hill showed that when a colored solution was injected into the subarachnoid space it appeared in the urine in from ten to twenty minutes, but that the cervical lymph-glands were only slightly tinged after one or two hours. He concluded that absorption was directly into the blood.

We performed a series of experiments to determine the manner of absorption of cerebrospinal fluid. A cannula was placed in the thoracic duct and phenolsulphonephthalein was substituted for cerebrospinal fluid. The total lymph was collected, and the output of phenolsulphonephthalein in the urine was estimated.

EXPERIMENT 3.—April 18, 1911. Thoracic duct fistula. Ether anesthesia. The substitution of 1 c.c. (6 mg.) phenolsulphonephthalein for 1 c.c. cerebrospinal fluid (through the occipito-atlantal membrane). Catheterization of bladder.

Time of injection, 12:03 p. m.; first appearance in urine, 12:09—six minutes; first appearance in lymph, 1:45—one hour, thirty-six minutes.

Excretion of phenolsulphonephthalein in urine: First hour, 1:09 p. m.—9.5 per cent.; second hour, 2:09—12.2 per cent.

From this experiment it is evident that the cerebrospinal fluid is excreted in the urine long before it appears in the lymph, and that in two hours over 21 per cent. (even with an anesthetic) is excreted in the urine, while only a bare trace is present in the lymph. Presumably absorption took place directly into the blood. Proof of this is supplied by experiments, of which the following is an example:

EXPERIMENT 4.—April 30, 1913. Thoracic duct fistula. Chlorbutanol anesthesia. *Specimens of blood* taken from the carotid artery. Substitution 1 c.c. (30 mg.) phenolsulphonephthalein for 1 c.c. cerebrospinal fluid, through the occipito-atlantal membrane.

Time of injection, 3:30 p. m. The results are given in Table 3.

TABLE 3.—RESULTS IN EXPERIMENT 4

Time	Blood Examination	Lymph Examination
3:32 p. m.	0	0
3:33 p. m.	+	0
3:36 p. m.	+	0
3:58 p. m.	+	0
4:15 p. m.	+	0

Animal killed with ether.

Absorption took place directly into the blood and was very rapid. The dye was detected in specimens of arterial blood in three minutes, whereas there was no trace in the lymph after forty-five minutes. In one experiment of a similar nature a trace was found in the lymph in eighteen minutes after injection. In no case was there more than a trace even at the end of two hours—a striking contrast to the content in the blood and urine. The trace of color in the lymph appearing after a considerable interval might readily be derived from the blood.

It may be objected that absorption had taken place through the tributaries of the right lymphatic duct. For this reason the following experiment was performed:

EXPERIMENT 5.—May 10, 1911. Ether anesthesia. Thoracic duct fistula; dorsal laminectomy, the spinal cord and dura ligated at level of fifth dorsal vertebra. As a further precaution a second ligation was made 2 cm. above the first. Injection of 1 c.c. (30 mg.) phenolsulphonephthalein into the subarachnoid space of the segment distal to both ligations. Time of injection, 2:06 p. m.

Blood examination, 2:12 p. m., +; 2:20 p. m., +.

Lymph examination, 2:12 p. m., 0; 2:20 p. m., 0.

Animal killed with anesthetic.

It is therefore evident from these experiments that the lymphatics play no part in the absorption of the cerebrospinal fluid, but that absorption takes place directly into the blood.

V. ABSORPTION IS A DIFFUSE PROCESS INVOLVING THE ENTIRE SUBARACHNOID SPACE

The preceding experiment shows that absorption takes place also from the spinal subarachnoid space. When phenolsulphonephthalein is injected into the cisterna magna it is, as will be shown subsequently, distributed to all parts of the cerebral and spinal subarachnoid space in a very short time. It is believed by some that absorption is limited to the superior longitudinal and the other venous sinuses, and that the remaining cerebral and spinal vessels take no part in this absorption. In order to determine the part of the spinal subarachnoid space in the absorption of cerebrospinal fluid, experiments like the following were done:

EXPERIMENT 6.—June 2, 1911. Dorsal laminectomy; chlorbutanol anesthesia; ligation of dura and cord at the level of the fourth thoracic vertebra. A second ligature was placed 2.5 cm. above the first, to prevent absolutely the direct transmission of fluid from the lower segment into the cranial subarachnoid space. Fluid withdrawn from distal spinal segment and substitution of 1 c.c. (12 mg.) phenolsulphonephthalein. Animal killed with anesthesia.

Time of injection, 12:47 p. m.; time of appearance in urine, 12:53 p. m.—six minutes; 18.2 per cent. was excreted the first hour and 10.4 per cent. the second hour.

EXPERIMENT 7.—Similar to Experiment 6. June 8, 1911.

Time of injection, 2:32 p. m.; time of appearance in urine, 2:38 p. m.—six minutes; 15.1 per cent was excreted the first hour and 13.2 per cent. the second hour.

Animal killed with anesthesia.

It will be seen that there is a very high absorption from the spinal subarachnoid space; in fact, the amount of phenolsulphonephthalein excreted is nearly as much as from the entire subarachnoid space. There is, however, with such experiments an increase in pressure which cannot be prevented. The spinal subarachnoid space in the dog contains comparatively little fluid, so closely do the arachnoid and dura envelop the spinal cord. For this reason it is impossible accurately to substitute the amount of fluid which is withdrawn. The injection is consequently under tension, which must alter the rate of absorption and probably accounts for the rapid excretion. This permits the deduction that an active and rapid absorption takes place from the spinal subarachnoid space. Absorption is, therefore, a diffuse process. It takes place from the entire subarachnoid space and is not restricted to any particular portion of this space. Our results, therefore, show that the absorption of cerebrospinal fluid is directly into the capillary network of the entire subarachnoid space.

VI. THE EVIDENCE AGAINST THE ABSORPTION BY MEANS OF STOMATA

The principal exponents of the theory of stomata as a means for the absorption of cerebrospinal fluid are Böhm, Adamkiewicz, Reiner and Schnitzler. The strongest argument in favor of stomata is that granules have been observed to pass from the subarachnoid space into the veins. This can readily be shown in embryos, and with much greater difficulty in adults; but as mentioned above, and as shown by Mall, this is entirely dependent on pressure and the consequent tearing or rupturing of delicate tissues.

Stomata in the subarachnoid space were originally suggested by Böhm (1869), but his observations lack confirmation. Stomata in lymphatics of the central tendon of the diaphragm, as described by von Recklinghausen, have been proved to be artefacts. That there are stomata in blood-vessels is even more difficult to believe. If there were stomata in the blood-vessels in the subarachnoid space one would expect to find bloody cerebrospinal fluid as the result of venous congestion. The absence of blood cannot be explained by valves, as these have never been demonstrated.

In our experiments, India ink and lampblack *granules in suspension were substituted for an equal amount of cerebrospinal* fluid, and the animals used were kept under anesthesia for varying periods of time. Even after two or three hours there was no evident egress of granules. Specimens of blood from superior longitudinal sinus were examined microscopically at frequent intervals for granules, but with uniformly negative results. At the end of one, two or three hours there was a perfectly uniform distribution of granules throughout the entire cerebral and spinal subarachnoid space. There was no evidence of an accumulation in any particular locality. A number of the animals were frozen, and subsequently placed in formaldehyd solution; the sinuses were later opened, examined by sections and the blood in the sinuses also examined. Granules were present in the pacchionian granulations and along the walls of the longitudinal and other sinuses, but there was no suggestion of any passage into the lumen of the sinus. In each case the granules were separated by the arachnoid membrane and a layer of dura.

The blood in the sinuses was also free from granules. That granules of this size never pass out of the subarachnoid space is not maintained. In all probability there is an elimination by some vital activity, but evidently not by a free transit through preformed openings.

Further evidence of the absence of stomata is offered by a number of experiments in which pressure was used. If granules are injected into the subarachnoid space of adult dogs under a pressure of 100 mm.

of mercury or less there is no passage of the granules into the venous sinuses. These high pressures kill the animal. The longitudinal and lateral sinuses can then be exposed for their entire distance, but even after the lapse of an hour or even longer granules are not found in the sinuses. The pacchionian granulations are full of granules, but there is no passage through their walls. It is evident, therefore, that with the animals' own processes of absorption during life and even with highly artificial pressures after death, no evidence can be obtained of a passage of granules, by way of stomata, either into the sinuses or into any other part of the vascular system.

It has been shown in the foregoing experiments that absorption is by a general or diffuse process involving the capillaries in the entire subarachnoid space. Since the absorption from the spinal subarachnoid is *at least proportionally as great* as from the entire subarachnoid space, it is not necessary to attempt to explain the absorption of cerebrospinal fluid by means of stomata along the cerebral venous sinuses.

VII. THE EVIDENCE AGAINST THE ABSORPTION OF CEREBROSPINAL FLUID BY THE PACCHIONIAN GRANULATIONS

The theory that the pacchionian granulations play a part in the absorption of cerebrospinal fluid is due to the work of Key and Retzius. This view has received much support. The pacchionian granulations are really arachnoid diverticula which project into the lumen of the sinuses and into the bones of the vault of the skull. They are lined by a layer of arachnoid with a superimposed layer of dura, which is a far greater mechanical impediment to the passage of fluid than the simple endothelium lining of the capillaries in the pia arachnoid. The pacchionian granulations, moreover, are not present at birth or are developed so poorly as to escape notice. They increase in size and number with age and with intracranial pressure.[7] It is asserted that in many animals they are absent.

Any evidence of the passage of fluid through the pacchionian granulations during life would be very difficult, if not impossible to obtain. Consequently, all proof is dependent on post-mortem injections. In such a condition it is possible to force fluid through the pacchionian granulations into the sinuses with very high pressure. Under a still higher pressure it is even possible to force water from the subarachnoid space into the nasal cavity.

The best evidence against the absorption of cerebrospinal fluid through the pacchionian granulations is the general character of the absorption from the subarachnoid space.

VIII. COMPARISON OF ABSORPTION OF CEREBROSPINAL, PERITONEAL AND PLEURAL FLUIDS

The absorption of fluids from the peritoneal and pleural cavities has been studied by Dandy and Rowntree. They showed that absorption of fluids from these spaces was a diffuse process, and was not dependent on the posture assumed. It was also demonstrated that absorption was directly into the blood and that lymphatics played no part. The absorption from these cavities is much more rapid than from the subarachnoid space. A comparison between the absorption

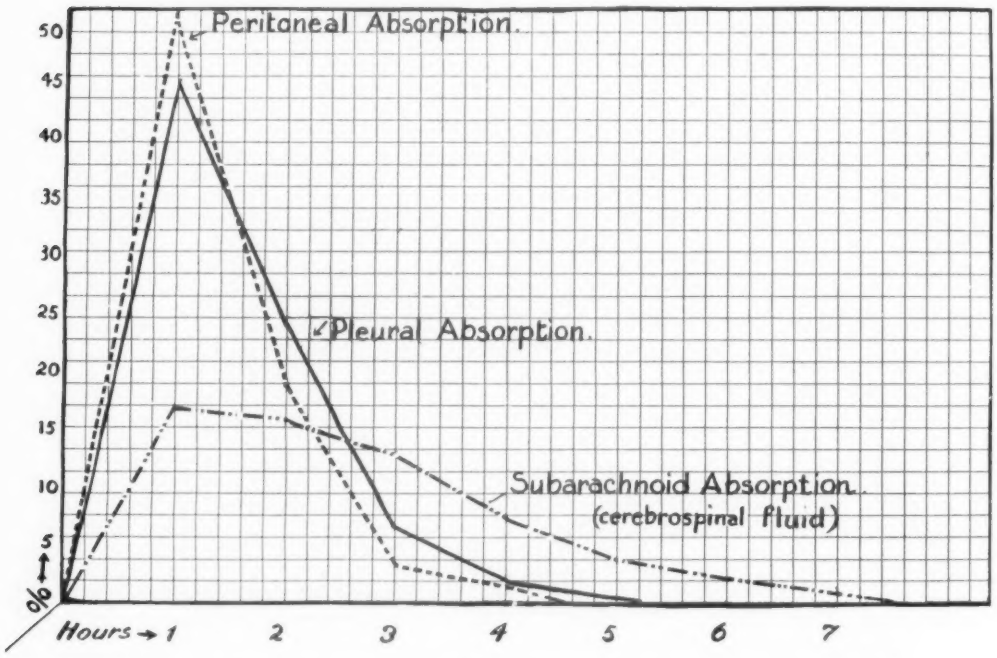

Fig. 7.—Curves to compare the total excretion of peritoneal, pleural and cerebrospinal fluids. The base line represents time divided into one-hour intervals. The vertical line represents absorption (percentage of excretion) of phenolsulphonephthalein in the urine.

of fluid from the pleural and peritoneal cavities with that from the subarachnoid space is shown in the accompanying chart. The time of first appearance of phenolsulphonephthalein in the urine was practically the same in all. The output from the pleural and the peritoneal cavities was more rapid than that from the subarachnoid space (Fig. 7).

IX. ABSORPTION FROM THE VENTRICLES

In order to complete the discussion of the absorption of cerebrospinal fluid it is necessary to consider briefly here some of the clinical observations, the details of which are given in a subsequent part of this article. In seven cases of hydrocephalus the communication between the ventricles and the subarachnoid space was found to be totally obstructed. An excellent opportunity to estimate absorption from the ventricles was thus allowed. When phenolsulphonephthalein was introduced into the ventricles of these patients its first appearance in the urine was greatly delayed (thirty or forty minutes or longer) and never was there an elimination of more than 1 per cent. during the two hours following the first appearance in the urine. This was irrespective of the dilatation of the ventricles or the quality of fluid present.[3]

The excretion of phenolsulphonephthalein after such an injection continued ten days and even longer. The dye was present in the ventricles also for the same length of time. It is evident, therefore, that practically *no absorption takes place from the ventricles.*

6. COMMUNICATION BETWEEN THE VENTRICLES AND THE SUBARACHNOID SPACE

The preceding experiments show that fluid forms in the ventricles and that it is absorbed from the entire subarachnoid space. It is evident that the normal balance between the production and the absorption of cerebrospinal fluid depends on an adequate communication between the place of formation and the place of absorption, namely, between the ventricles and the subarachnoid space.

Six foramina of communication between the ventricles and the subarachnoid space have been described. The foramen or canal of Bichat was first described (1819) as a median opening accompanying the vena Galena magna and affording communication between the third ventricle and the subarachnoid space. Soon afterward, Bichat added a foramen at the tip of each lateral ventricle—the lateral foramina of Bichat. Magendie, Luschka, and Key and Retzius proved these three foramina to be artefacts, as they were evident only after pressure was used. Mierzejewsky and Merkel (1872) again asserted the existence of a foramen from the tip of each lateral ventricle. Though regarded by most anatomists as artefacts, they are still believed by many to exist.

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3. That tension of the intraventricular fluid has no effect on the absorption from the ventricles is shown by the fact that before and after the removal of 90 c.c. of ventricular fluid in Case 4, N. M., Group 1, the absorption was exactly the same (0.25 per cent. in two hours).

Though a communicating foramen at the fourth ventricle was suspected by Cotugno and others, its existence was first demonstrated by Magendie in 1825. Renault (1829) proved that no such foramen existed in the horse and that hydrocephalus in this animal did not result from its absence. Magendie confirmed the findings of Renault, though he continued to maintain the importance of this foramen in man. Krause (1843) maintained that all the ventricles, including the fourth, were sealed by pia, and that the foramen of Magendie was an artefact produced either by pressure or by dissection. Todd (1847) and Reichert (1861) expressed similar views. Virchow (1854) strongly opposed the theory of the existence of the foramina and of any communication between the ventricles and the subarachnoid space or between the cerebral and the spinal subarachnoid spaces. "There is no direct communication between the subarachnoid spaces, either between each other or with the cavities of the brain, and the fluid contained in them cannot thus simply rise or fall."[4] The weight of his teachings was sufficient to retard greatly the acceptance of Magendie's views.

The existence of the foramen of Magendie was, however, supported by capable anatomists. Luschka (1854) verified the absence of this foramen in the horse and thought that the absence of hydrocephalus was explained by the lateral foramina which he described. These foramina are present in all animals and are larger in those in which there is no central foramen. He unquestionably substantiated the existence of the central foramen and named it in honor of Magendie. Key and Retzius (1875) confirmed the findings of Magendie and Luschka in every particular.

Retzius in 1896 examined one hundred brains and found the foramen of Magendie absent in two and the foramina of Luschka absent in three. This was confirmed by Hess and Cruveilhier. Cannieur (1898), however, after numerous injections and histological studies, concluded that the evidence in favor of communication could be explained by artefacts and that the ventricles formed a closed system everywhere lined by ependyma. Testut also believed this. Schmorl expressed a similar view after noting serological differences between the fluid in the ventricles and the subarachnoid space. He believed that this not only denoted a double origin of cerebrospinal fluid, but that the absence of the foramina of Magendie and Luschka was to be deduced therefrom.

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4. "Die subarachnoidealen Raüme stehen in keiner offenen Verbindung, weder unter sich, noch mit den Hirnhöhlen, und die in ihnen enthaltene Flüssigkeit könne daher nicht einfach in ihnen auf-oder absteigen."

We do not think that observations of a similar character can throw any additional light on this subject. The experiments which follow prove the existence and the function of these foramina between the ventricles and the subarachnoid space.

I. THE DEMONSTRATION OF FUNCTIONAL COMMUNICATION

When phenolsulphonephthalein is introduced into the ventricles, it appears in the spinal fluid in from one to seven minutes. In these cases there was no increased tension of the ventricular fluid and no pressure was used. The results can therefore be attributed only to the normal means of regulating the distribution of fluids. The time of appearance of the dye in the spinal fluid may occasionally be delayed in cases of hydrocephalus even when there is free communication (Case 3).

TABLE 4.—TIME OF APPEARANCE OF PHENOLSULPHONEPHTHALEIN IN THE SUBARACHNOID SPACE FOLLOWING ITS INTRODUCTION INTO THE VENTRICLES

Case 1	2 minutes
Case 2	7 minutes
Case 3	13 minutes
	20 minutes
Case 4	1 minute

When phenolsulphonephthalein is substituted for an equal amount of *spinal fluid* and introduced into the spinal subarachnoid space, the dye is soon found *in the ventricles.* These observations demonstrate that an open communication exists between the ventricles and the subarachnoid space in both directions. They also demonstrate that fluid readily passes upward into the ventricles even against the stream of cerebrospinal fluid from the ventricles. Such results render untenable the theory, usually credited to Key and Retzius and recently advocated by Propping, that valves, though not demonstrable, exist at these openings. The passage of fluids from the subarachnoid space into the ventricles is of the greatest importance in its bearing on intraspinal anesthesia and the treatment of diseases of the central nervous system by intraspinal injections.

II. THE LOCATION OF THE COMMUNICATION

If an obstruction exists either at the aqueduct of Sylvius or at the basal foramina of Magendie and Luschka, phenolsulphonephthalein, after introduction into the ventricles, does not appear in the spinal fluid. This was the case in seven patients, and the obstruction was found in four on whom post-mortem examination was held.

This proves that there are no openings between the third and lateral ventricles and the subarachnoid space, or in other words, that the foramina of Bichat and Mierzejewsky (or the lateral foramina of Bichat) do not exist. The aqueduct of Sylvius is the only channel for the escape of fluid from the third and lateral ventricles. The openings between the ventricles and the subarachnoid space must therefore be posterior to the aqueduct of Sylvius and must lead from the fourth ventricle. These openings are the foramina of Magendie and Luschka.

7. THE DISTRIBUTION OF GRANULES IN THE SUBARACHNOID SPACE

Those who favor the theory of absorption of cerebrospinal fluid by means of stomata or by specialized structures along the longitudinal or other sinuses have assumed the presence of an intra-arachnoidal current to carry the cerebrospinal fluid to these structures. This is very similar to the assumption that an intraperitoneal current carries the fluids to the central tendon of the diaphragm. We have been unable to find any evidence to support such an assertion either in the peritoneal cavity (Dandy and Rowntree) or in the subarachnoid space.

To determine the presence or absence of a current in the subarachnoid space, we substituted for the cerebrospinal fluid (withdrawn through the occipito-atlantal membrane) an equal amount of a suspension of lampblack granules. The animal was kept under anesthesia from one to two hours, and at the end of this time was killed and frozen to avoid distribution of the granules after death. Subsequent examination showed a most uniform distribution of granules throughout both the cerebral and spinal subarachnoid space. In so far as could be determined there was absolutely no evidence of any accumulation along the sinuses or in any other locality. With the exception of four parts of cranial nerves, there were no granules along the nerve sheaths. Granules were present in the olfactory nerves to their termination, the optic nerves to the fundus, the trigeminus over the gasserian ganglion and the auditory nerve to the internal auditory meatus. This distribution represents the normal limits of the distribution of the cerebrospinal fluid. If pressure is used, and only then, the other cranial and spinal nerves may be injected for varying distances.

The even and quite rapid distribution of granules throughout the cerebrospinal fluid is more readily explained by the pulsation in the central nervous system.

Part 2.—Clinical and Pathological Studies

In the following observations we determined the amount of absorption from the ventricles, the amount of absorption from the subarachnoid space and whether or not there was free communication between the ventricles and the subarachnoid space. Phenolsulphonephthalein[5] was used in these studies. After the introduction of a phenolsulphonephthalein solution into the ventricles and, at a subsequent test, into the subarachnoid space, the time of its first appearance in the urine was determined and the amount which was excreted in the urine for a two-hour period was estimated. The patency or occlu-

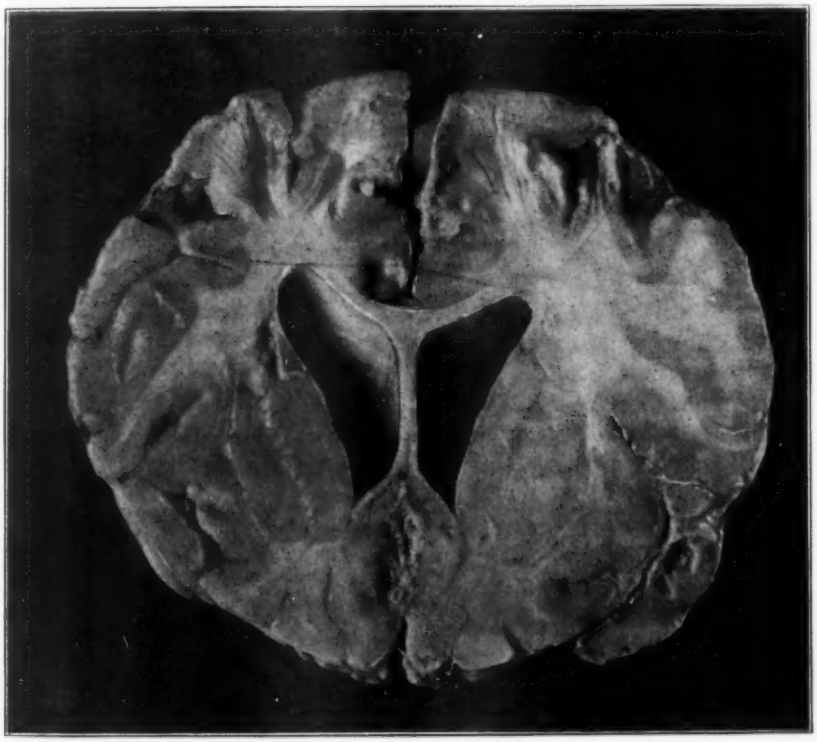

Fig. 8.—Brain, cross-section of a normal child of 1 year; included as a standard for comparison with specimens of internal hydrocephalus which follow.

5. It should be emphasized that the ordinary solution of phenolsulphonephthalein is made up with alkali; this is sufficient to prevent its use in the central nervous system. We used a neutral solution which, when diluted with cerebrospinal fluid, caused no symptoms whatever referable to the central nervous system. For ventricular use, 1 c.c. (6 mg.) of phenolsulphonephthalein was diluted with 3 c.c. of cerebrospinal fluid and for spinal subarachnoid use 1 c.c. (6 mg.) of phenolsulphonephthalein was diluted with 2 c.c. of cerebrospinal fluid.

sion of the communication was determined by the presence or absence in the spinal fluid of the phenolsulphonephthalein after its introduction into the ventricles.

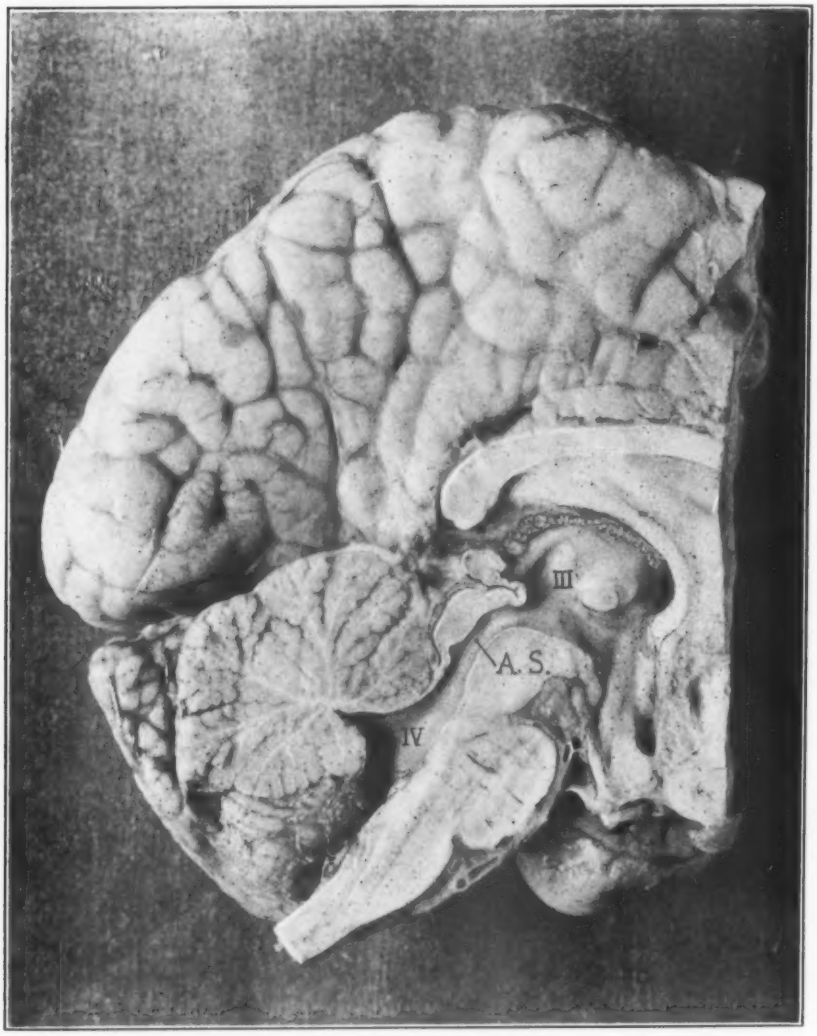

Fig. 9.—Midsagittal section of brain shown in Figure 8. Note the patent foramen of Magendie and the aqueduct of Sylvius.

8. *ABSORPTION FROM THE VENTRICLES AND THE SUBARACHNOID SPACE WHEN HYDROCEPHALUS DOES NOT EXIST*

In a number of patients in whom a ventricular or lumbar puncture was indicated for diagnosis, phenolsulphonephthalein was substituted

for the cerebrospinal fluid removed. From these results a normal standard of absorption from the ventricles and the subarachnoid space and the average time of normal communication between them were obtained.

It was found that after introduction into the ventricles, phenolsulphonephthalein appeared in the urine *in from ten to twelve minutes, and that during two hours from 12 to 20 per cent. was excreted.* When introduced into the subarachnoid space it appeared in the urine in *from six to eight minutes, and from 35 to 60 per cent. was excreted in two hours.* Phenolsulphonephthalein passed rapidly from the ventricles to the subarachnoid space, and appeared in the spinal fluid in from *one to three minutes.*

Pathological studies have shown that in some cases of hydrocephalus the communication between the ventricles and the subarachnoid space is open and that in others it is closed. It is obvious that a different operative procedure is indicated in these different types of cases. The inability to decide which type is present is undoubtedly one reason why the results of operation have been so unsatisfactory. We have endeavored to determine the presence or absence of the communication in hydrocephalus by the use of phenolsulphonephthalein after having demonstrated on animals that the method was harmless. In all cases permission for applying the tests was obtained from the parents.

9. *STUDIES OF THE ABSORPTION FROM THE VENTRICLES AND THE SUBARACHNOID SPACE IN PATIENTS WITH INTERNAL HYDROCEPHALUS*

It was possible to divide the cases which we studied into two groups. The introduction of phenolsulphonephthalein into the ventricles and a later examination for this substance in the spinal fluid will determine either by its absence that the communicating foramina are occluded (Group 1) or by its presence that they are patent (Group 2).

GROUP 1. — INTERNAL HYDROCEPHALUS WITH OBSTRUCTION TO THE CHANNELS OF EXIT FROM THE VENTRICLES

CASE 1.—P. G., aged 7 months. Diagnosis: General miliary tuberculosis, tuberculous meningitis; internal hydrocephalus secondary to meningitis; meningocele.

Clinical Note.—Family History: Two other children living and well. No family history of hydrocephalus.

Past History: Full term, normal delivery. The patient was born with a meningocele. Dentition began at 3 months. Sat up at fourth month. No acute illness. No apparent disturbance from meningocele.

Present Illness: The patient had a severe cough and fever and had been very drowsy for a week.

Physical Examination: The patient was a well-nourished infant lying in a state of coma. In the sacral region was a large meningocele. Compression of the tumor caused bulging of the anterior fontanel. Von Pirquet test, positive.

Spinal Fluid from Meningocele: Clear fluid, 112 cells per cubic millimeter; tubercle bacilli present.

Tests.—1. There was no evidence of communication between the ventricles and the spinal subarachnoid space in forty-five minutes. 2. After ventricular introduction phenolsulphonephthalein did not appear in the urine for forty-five minutes. *In two hours only 0.75 per cent. was excreted.* It was being excreted seventy hours later. 3. The absorption from the spinal subarachnoid space was

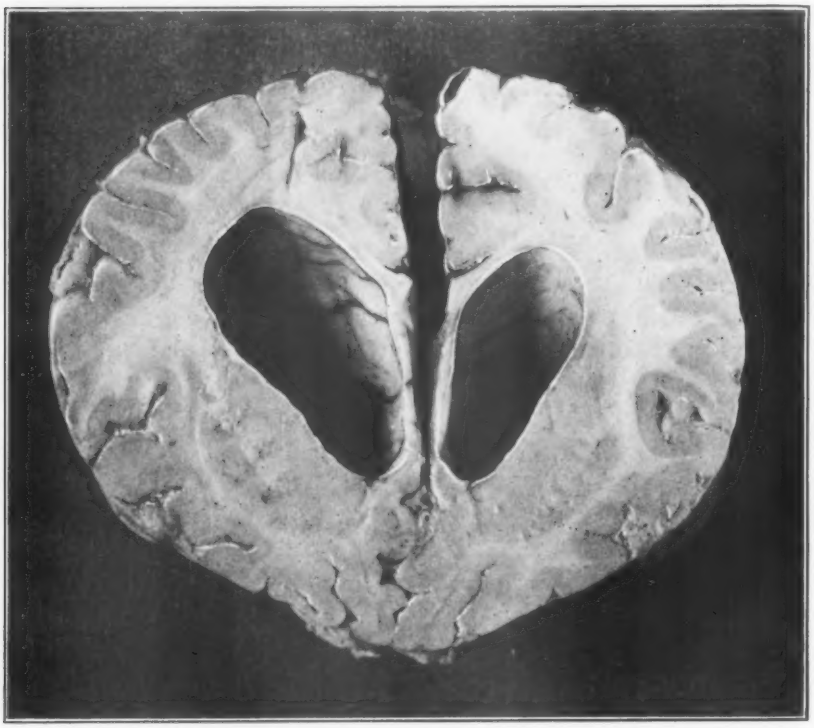

Fig. 10.—Cross-section of brain, showing moderately dilated lateral ventricles, in acute internal hydrocephalus (Case 1, Group 1, P. G.) due to occlusion of the foramina of Magendie and Luschka by a tuberculous exudate. There was no absorption from the ventricles.

rapid. Phenolsulphonephthalein first appeared in the urine six minutes after its introduction into the ventricles, and *62 per cent. was excreted in the first two hours.*

Death from tuberculous meningitis.

Pathological Findings.—General miliary tuberculosis; tuberculous meningitis; myelomeningocele; internal hydrocephalus. The brain was normal in size. There was a plastic exudate over both parietal lobes, along the falx cerebri and the sylvian arteries, and scattered over the cerebral cortex were numerous tubercles. The base of the brain was covered with a thick exudate which extended from the optic chiasm posteriorly over the inferior surface of the

pons and medulla, and the lower surface of both cerebellar hemispheres. The cisterna magna was filled with exudate. *The foramina of Magendie and foramina of Luschka were completely occluded by this exudate* (Figs. 10 and 11). On section, the ventricles were moderately dilated. A sagittal section continued through the midline showed the foramen of Monro to be moderately dilated, and the aqueduct of Sylvius patent. The fourth ventricle was about normal in size, and was partly filled with tuberculous exudate. This exudate, in addition

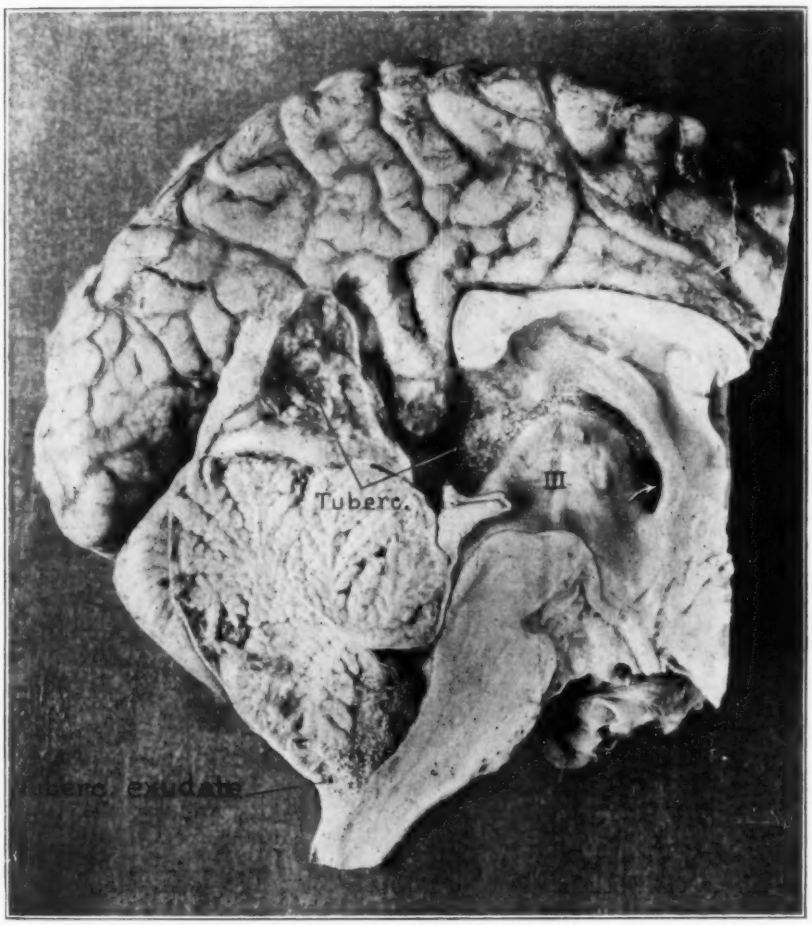

Fig. 11.—Midsagittal section of brain in Case 1. Observe the exudate which completely fills the space between the medulla and cerebellum and binds them together. This completely blocked the foramina of Magendie and Luschka. The aqueduct of Sylvius is patent.

to forming an external covering, firmly bound the medulla and the cerebellum together, thus doubly sealing the foramina of exit. It was also continuous with that which extended over the surface of the cerebellum and the base of the brain. Many tubercles were scattered over the ependyma of the third and of the lateral ventricles. The choroid plexus appeared normal except for tubercles

demonstrated histologically. The pineal gland was very small, measuring about 2 mm. in diameter. The vein of Galen was patent.

The spinal cord and its meninges did not appear abnormal, except for a few miliary tubercles; no exudate was present. *Meningocele:* The sac measured 8 by 7 cm. It projected through a median defect in the first and second sacral vertebrae and was firmly attached to the bodies of these vertebrae by a small pedicle 1.5 cm. in length. The cord ended at the upper part of the meningocele; the filum terminale and a few branches of the cauda crossed the cavity of the meningocele and became embedded in a cicatrix on the dorsal wall. The sac of the meningocele was directly continuous with the subarachnoid space.

CASE 2.—A. H., aged 6 months. Diagnosis: Internal hydrocephalus, myelomeningocele (ruptured).

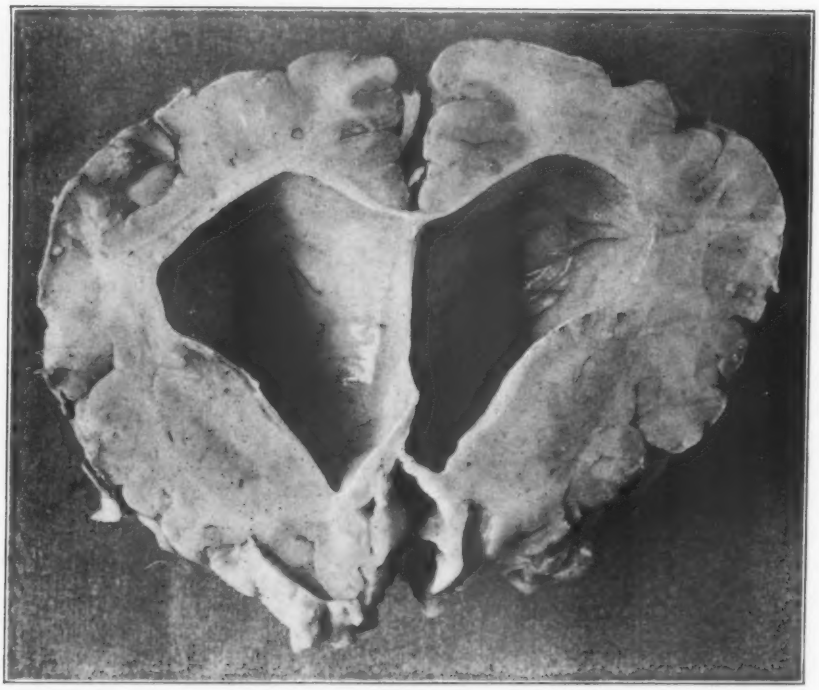

Fig. 12.—Cross-section of brain to show greatly distended lateral ventricles in case of internal hydrocephalus (Case 2, Group 1, A. H.) due to complete occlusion of the aqueduct of Sylvius.

Clinical Note.—Past History and Present Illness: Only child, full term, normal delivery. At birth the mother noticed a "swelling" the size of an apple over the lower part of the spine (meningocele), and the head appeared to be larger than normal. The baby had never moved her legs. The head and the swelling on the back had steadily increased in size. Three days before admission the meningocele ruptured, after which there was a discharge of slightly blood-tinged fluid with consequent diminution in the size and in the tension of the sac.

Physical Examination: The patient was a fairly well-nourished infant with a moderate degree of hydrocephalus. The head measured 40 cm. in circumference. The anterior and posterior fontanels and the sutures were widely open.

There was a downward dislocation of the eyes and a nystagmus in all directions. The neck was rigid and the arms slightly spastic. The lower extremities were flaccid and atrophied; the reflexes were absent. A collapsed meningocele sac was present in the lower lumbar and sacral region. From the ruptured medullovascular area a turbid, slightly blood-tinged fluid exuded.

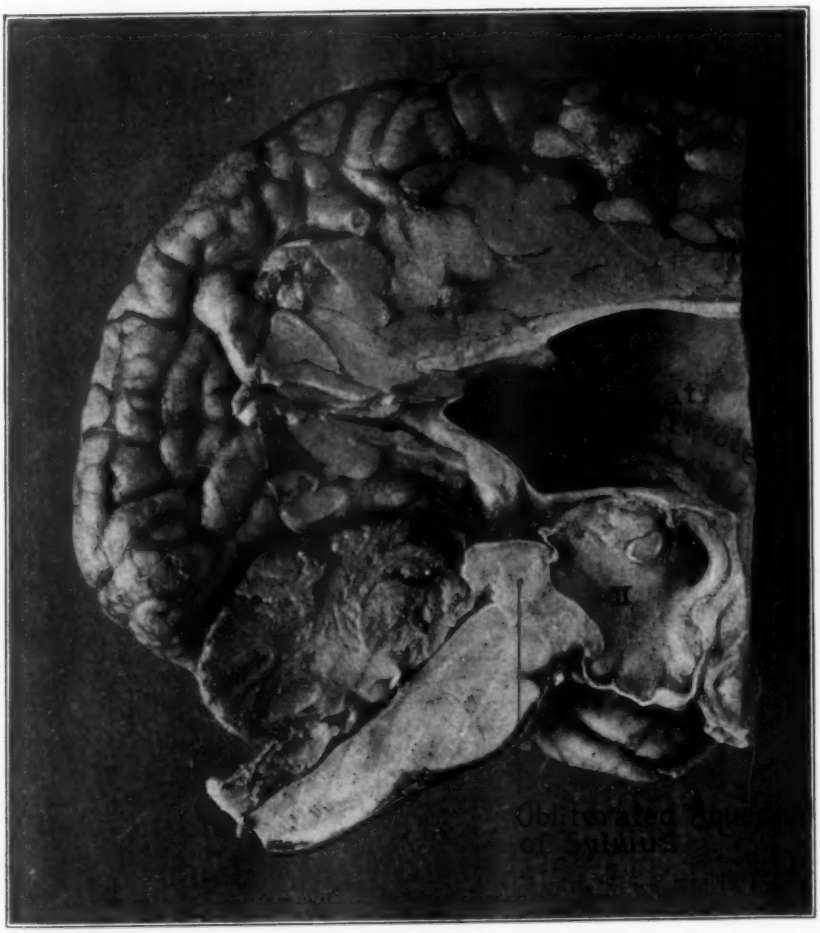

Fig. 13.—Midsagittal section of brain in Case 2 to show complete absence of the aqueduct of Sylvius and its replacement by neuroglia. Note the greatly dilated third and lateral ventricles anterior to the obstruction and the flattened slit-like fourth ventricle posterior to the obstruction. The septum lucidum is almost completely atrophied.

Tests.—1. There was no evidence of communication between the ventricles and the spinal subarachnoid space *in two hours.* 2. *Forty minutes* after ventricular introduction of phenolsulphonephthalein it had not appeared in the urine. *In two hours only 1 per cent. was excreted* in the urine.

Death occurred as a result of the rupture of the meningocele sac.

Pathological Findings.—The brain was enlarged. The sulci were shallow and the convolutions flattened. The meninges appeared normal, the foramina of Luschka and Magendie were patent. The lateral and third ventricles were greatly and uniformly dilated, the relative and absolute size of which are shown in the photographs (Figs. 12 and 13). The fourth ventricle was flattened to a mere slit.

The aqueduct of Sylvius was completely obliterated. There was a small blind pouch at the position where the aqueduct should begin from the third ventricle, but beyond this there was no gross evidence of its presence. Cross

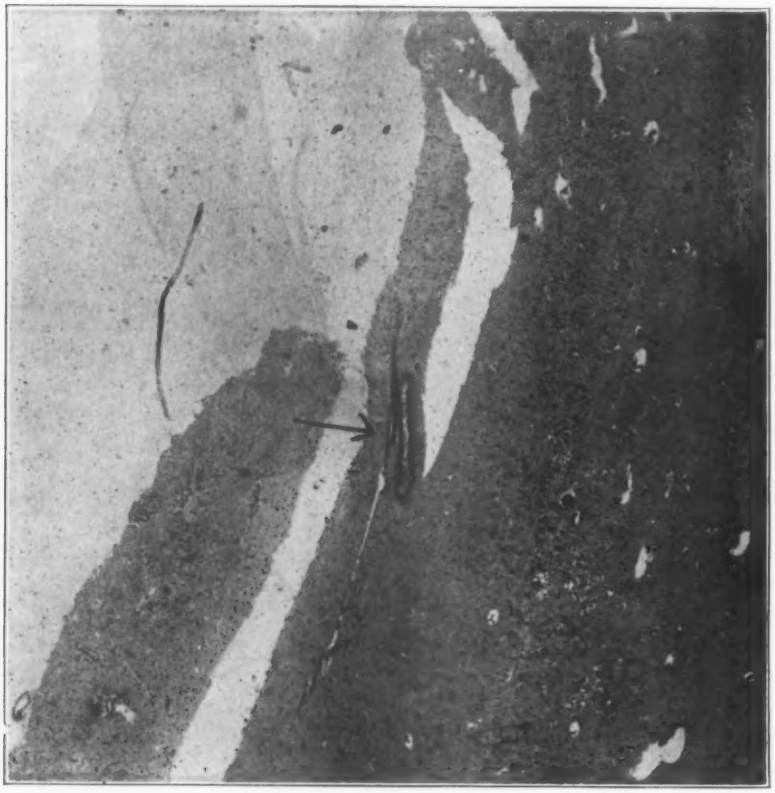

Fig. 14.—Photomicrograph to show a microscopic remnant of the aqueduct of Sylvius in Case 2.

sections of the midbrain examined microscopically showed two independent, small spaces with a lining of ependymal cells. In one there was a small lumen and in the other the walls were in apposition. They undoubtedly represented remains of the aqueduct of Sylvius (Fig. 14). Microscopically there was a gliosis which had replaced the aqueduct of Sylvius. The corpora quadrigemina were very large but symmetrical.

The vena Galena magna was normal in size and the lumen was patent. The pineal gland was small. The choroid plexuses of the lateral ventricles were normal.

The meningocele sac measured 10 by 7 by 6 cm. It protruded through a defect in all the lumbar and the first sacral vertebrae and was attached by a broad base to these vertebrae. Its cavity was directly continuous with the subarachnoid space of the spinal cord. A series of from six to seven nerve roots rising from the cord at the line of attachment to the vertebrae ran transversely, on each side, through the cavity to the walls of the sac.

The spinal canal and subarachnoid space were otherwise normal.

Remarks.—The absence of communication was shown by the tests. This was substantiated by finding only microscopic remnants of the aqueduct of Sylvius. The dilatation of the third and lateral ventricles ahead of the obstruction and the collapsed fourth ventricle behind the obstruction were evidences of the influence of an obstruction in the aqueduct.

CASE 3.—N. P., aged 6 weeks. Diagnosis: Internal hydrocephalus.

Clinical Note.—Family History: Two other children aged 2 years and 4 years living and well. No history of syphilis or hydrocephalus.

Past History and Present Illness: Full term, normal delivery. At birth it was noticed that the child's head was large. When 2 weeks old she had general convulsions which lasted two or three days. Three weeks before death she had convulsions lasting over a period of three or four days. The head had grown progressively larger.

Physical Examination: The patient was an emaciated infant with hydrocephalus. The head measured 50.5 cm. in circumference. There was separation of nearly all of the cranial bones. There was displacement of the eyes downward and a nystagmus in all directions.

Tests.—1. There was *no evidence of communication* between the ventricles and the subarachnoid space *in twenty minutes.* 2. After ventricular introduction phenolsulphonephthalein did not appear in the urine in forty-five minutes. *During two hours only 1 per cent. was excreted.*

Death from internal hydrocephalus.

Pathological Findings.—The cortex in places was only a millimeter in thickness and the brain collapsed into a shapeless mass when it ruptured. Sulci were present only over the temporal lobes; the remaining cortex was smooth. The size of the ventricles was almost equal to that of the calvarium. The foramina of Monro were from five to six times the normal size. There was complete atrophy of the septum lucidum. The fourth ventricle and the basal foramina of Luschka and Magendie were normal; the meninges were normal; the cerebellum was greatly flattened anteroposteriorly, as the result of the pressure of fluid in the lateral ventricles.

There was no aqueduct of Sylvius (Fig. 15). No trace of the aqueduct of Sylvius could be found in the gross or in sections when examined under the microscope, nor was there any evidence of epithelial remains as in the previous specimen. The choroid plexus was small but otherwise appeared normal. The vein of Galen was unobstructed. The pineal body was small. The spinal cord and the meninges, cerebral and spinal, were normal.

CASE 4.—N. M., aged 24 months. Diagnosis: Internal hydrocephalus.

Clinical Note.—Family History: Three other children living and well. No history of hydrocephalus or syphilis.

Past History and Present Illness: Full term, normal delivery. The patient's head was "large and round" at birth, but until he was 4½ months old it was not considered abnormal in size. He never held up his head, sat up or walked. Dentition began at the twelfth month. The patient had had no illness suggestive of meningitis. A puncture of the corpus callosum was performed when the patient was 1 year old. The head continued to increase in size.

Physical Examination: The patient was a well-nourished child, with a very large head, which measured 54 cm. in circumference. The anterior fontanel was 10 by 9 cm. in diameter; it was tense and bulging. The sutures were widely

separated. There was ocular displacement downward, an internal strabismus of the left eye and a nystagmus in all directions. The eye-grounds showed optic atrophy. There was a slight spasticity of the arms and legs. The reflexes were exaggerated and there was an ankle clonus. The head increased 11 cm. in seven months. The child's condition otherwise remained the same except for a partial weakness of both arms and legs.

Blood: Wassermann reaction, negative.

Ventricular Fluid: Clear. Noguchi globulin reaction negative, 6 cells per cubic centimeter.

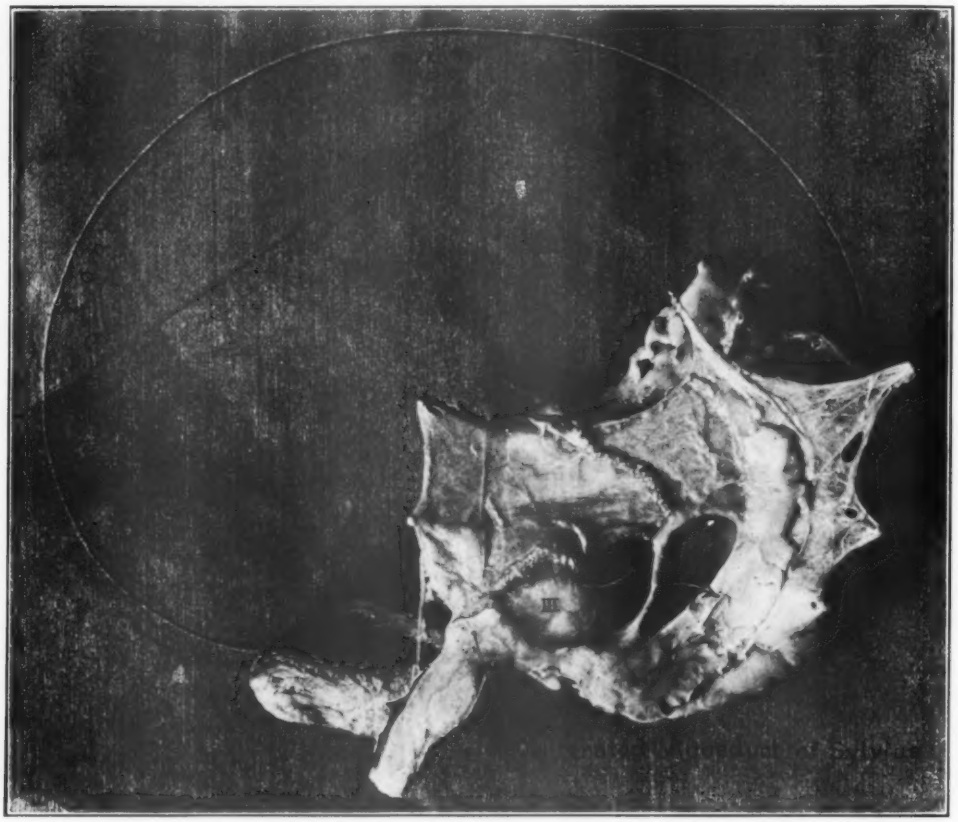

Fig. 15.—Advanced internal hydrocephalus (Case 3, Group 1, N. P.) caused by a completely occluded aqueduct of Sylvius. The cortex is a mere shell and could not be retained in its proper form. Note the exceedingly large foramen of Monro and the fringes of choroid plexus. Note the small fourth ventricle behind the occluded aqueduct of Sylvius, in marked contrast to the huge ventricles in front of this obstruction. The cerebellum is greatly flattened from the pressure of the distended lateral ventricles.

Tests.—1. There was no evidence of communication between the ventricles and the subarachnoid space in two days. 2. After ventricular introduction phenolsulphonephthalein did not appear in the urine for forty minutes. ***In two hours only 0.6 per cent. was excreted. Phenolsulphonephthalein was being excreted after eleven days.*** One month later, similar results were obtained.

Phenolsulphonephthalein appeared in the urine in thirty-five minutes and 0.5 per cent. was excreted in two hours. It was being excreted after eleven days. 3. After subarachnoid introduction, phenolsulphonephthalein appeared in the urine *in six minutes, and 35 per cent. was excreted in two hours.* After twenty hours there was no trace of phenolsulphonephthalein in the urine. 4. The kidney function was normal; 45 per cent. was excreted in two hours.

Remarks.—The results in this case were very similar to the one preceding: there was practically no absorption from the ventricle, and the appearance time of phenolsulphonephthalein in the urine was greatly delayed. In marked contrast were the results obtained from the subarachnoid space. It was evident that there was no communication between the ventricles and the subarachnoid space. The duration of excretion over eleven days in two separate experiments demonstrated the slow rate of absorption from the ventricles.

There could be no doubt that an obstruction existed either at the aqueduct of Sylvius or the basal foramina of Luschka and Magendie. We were never able to obtain more than 3 c.c. of cerebrospinal fluid by lumbar puncture. From the fact that so little spinal fluid could be obtained, we were inclined to infer that the obstruction was located at the basal foramina.

The patient is living.

Case 5.—M. R., aged 13 months. Diagnosis: Internal hydrocephalus.

Clinical Note.—Family History: Mother and father living and well. The patient was a third child; a brother aged 5 years and a sister aged 3 living and well. No history of syphilis; no history of hydrocephalus.

Past History and Present Illness: The child was born at full term; instrumental delivery. The patient was well until 4 months old. Then she had a severe illness, which lasted one month. The body was rigid; there was marked opisthotonus and many convulsions of a general character; during this time the patient had a high fever. The mother noticed an enlargement of the head three weeks after the onset of this illness. The following four months, the increase in the size of the head was rapid. After that it grew larger but not so rapidly.

Examination: The patient was a well-nourished child. The head measured 55.5 cm. in circumference. The fontanels were open. The sutures were widely separated. There was marked downward displacement of the eyes, so that the pupils were almost entirely hidden behind the lower lids. A lateral and vertical nystagmus was present. There was a low grade (1 to 2 diopters) bilateral choked disk. Von Pirquet test, negative.

Spinal Fluid: Clear, six cells per cubic centimeter; Wassermann, negative. Reducing substance (Fehling's), present.

Ventricular Fluid: Five c.c. clear fluid, two cells per cubic millimeter; Wassermann, negative; reducing substance (Fehling's), present.

Tests.—1. There was *no evidence of communication between the ventricles and the subarachnoid space in one and one-half hours.* 2. After ventricular introduction, phenolsulphonephthalein did not appear in the urine for twenty minutes. *Only 0.9 per cent. was excreted in two hours.* 3. After subarachnoid introduction, phenolsulphonephthtalein appeared in the urine in eight minutes; *25 per cent. was excreted in two hours.*

Patient died two months later of hydrocephalus.

Pathological Findings.—The brain was hardened *in situ* with formaldehyd solution. When removing the brain, an unusual accumulation of fluid filling the entire posterior cranial fossa was encountered. This could be likened to an encapsulated cyst. The walls were thin, transparent and in many places adherent to the dura. While freeing the lateral portions of the cyst, it was punctured and the brain collapsed. The cyst was a greatly dilated fourth ventricle, and the roof of the ventricle formed its walls (Fig. 16). Its size was limited only by the limitations of the posterior fossa. The cyst wall was adherent to the spinal cord and the lateral lobes of the cerebellum, making an impermeable membrane and preventing communication between the ventricles and the suba-

rachnoid space. The lateral lobes of the cerebellum were separated 4 cm. and between them stretched this impermeable membrane. The aqueduct of Sylvius was considerably dilated. The septum lucidum was atrophied; the third and lateral ventricles and the foramina of Monro were greatly dilated. Their relative size is best shown in the accompanying drawings[6] (Figs. 17 and 18).

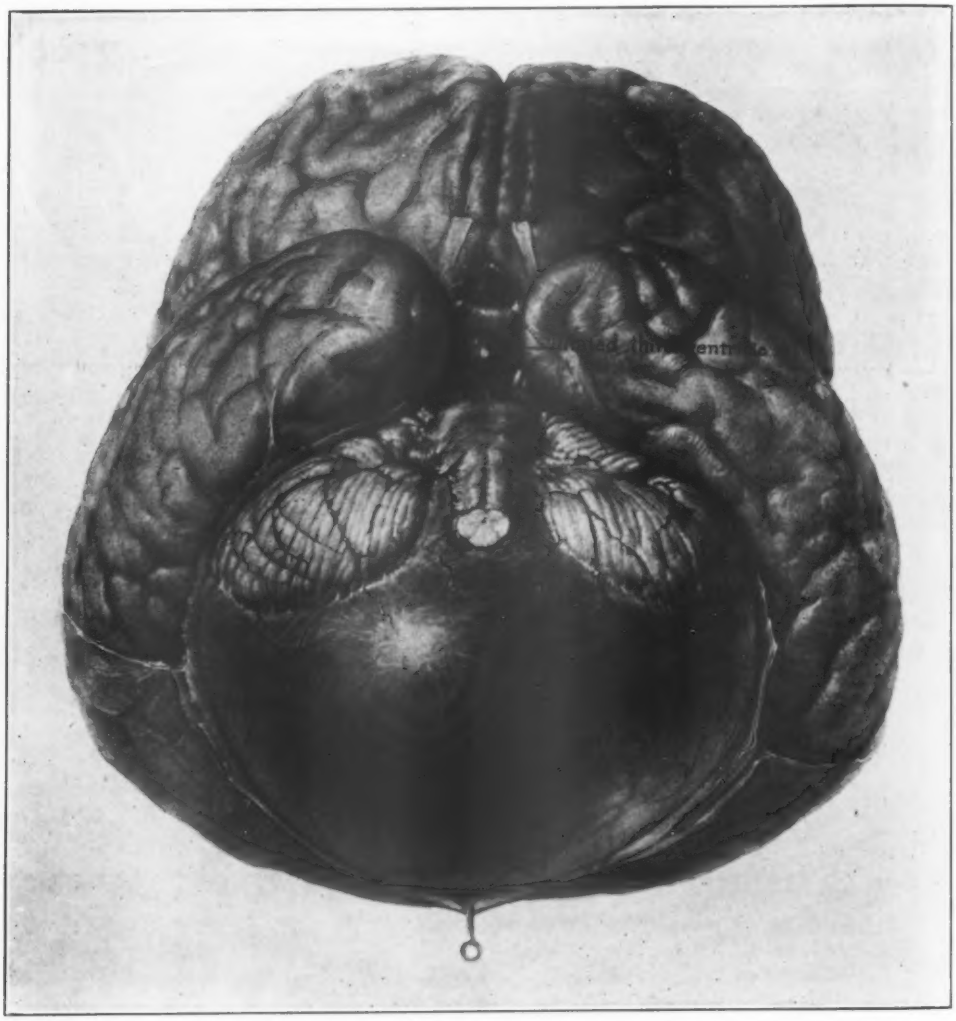

Fig. 16.—Ventral view of the brain in Case 5, Group 1, M. R. The foramina of Magendie and Luschka are absent and the fourth ventricle is distended into a huge cyst completely filling the posterior cranial fossa. The lateral lobes of the cerebellum are separated and crowded to either side. Note also the distended third ventricle.

6. We wish to express our thanks to Mr. Max Brödel for the accompanying drawings and for his assistance in the preparation of many of the figures.

The pia arachnoid was everywhere fused with the "cyst wall" of the fourth ventricle; this membrane was greatly thickened over the base of the brain. The usual transparent bridge of the pia arachnoid between the inferior surface of the pons and the optic chiasm was so opaque that the underlying brain was invisible; this opaque thickened membrane was also continuous over and adherent to the floor of the third ventricle. It also completely covered and was

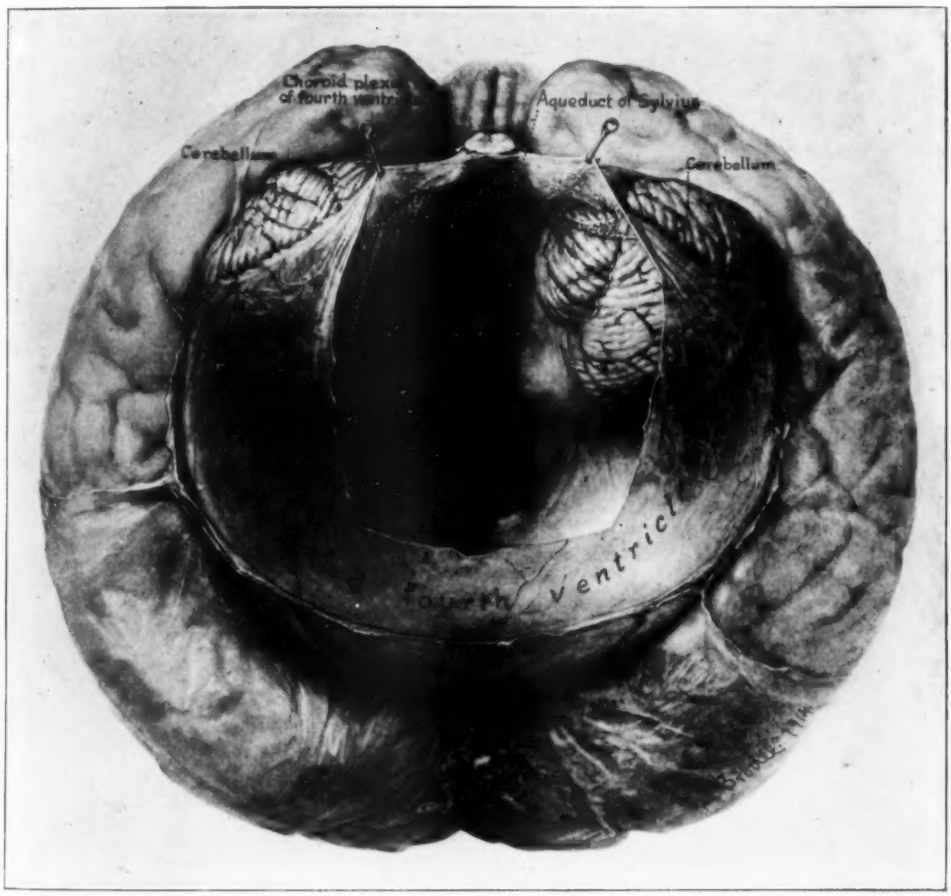

Fig. 17.—View of dilated fourth ventricle in Case 5 with window removed. Note the extent of the "cyst," the separation of the cerebellar hemispheres and the patent aqueduct of Sylvius.

adherent to the optic chiasm. Over the entire base of the brain this thickening of the meninges was very apparent; over the surface of the cerebral lobes it was less apparent.

The vein of Galen and the straight sinus were normal; the choroid plexuses appeared to be normal. The choroid plexus of the fourth ventricle was entirely within the cyst. The pineal gland was small. The spinal cord was not obtained for examination.

Remarks.—In this case also an absence of communication was demonstrated by the phenolsulphonephthalein test. This was confirmed by the post-mortem findings. There was practically no absorption from the ventricles and a rather high though subnormal absorption from the subarachnoid space. The partial obliteration by adhesions of the subarachnoid space over these areas mentioned no doubt explains the diminished absorption from this space.

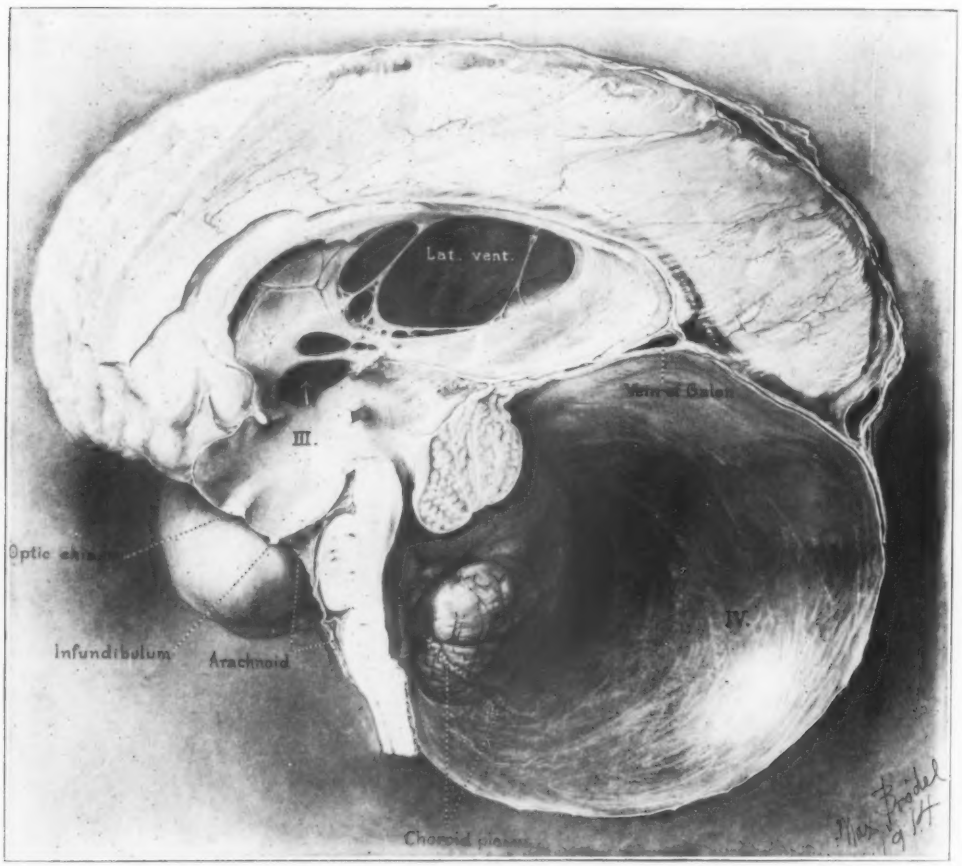

Fig. 18.—Midsagittal view of brain in Case 5. All the ventricles communicate freely with each other. There are no foramina of Magendie and Luschka. The choroid plexus is included in the "cyst." Note the patent and enlarged foramen of Monro (arrow) and aqueduct of Sylvius. The large openings in the septum lucidum show the effects of the intraventricular pressure.

Case 6.—F. W., aged 6 months. Diagnosis: Internal hydrocephalus. Meningocele and syringomyelocele.

Clinical Note.—Family History: The patient was the youngest of four children. The other three were well. There was no evidence of syphilis. No history of hydrocephalus.

Past History: Full term, difficult delivery, owing to large head, without instruments. Weight at birth, 10 pounds.

Present Illness: The mother noticed that the head was abnormally large at birth. There was also present a large "swelling" over the middle of the lower back. The circumference of the head and the swelling over the back gradually increased in size.

Examination: The patient was a well-nourished infant whose head measured 51 cm. in circumference. There was diastasis of the cranial bones. The anterior and posterior fontanels were widely open and tense. A large meningocele protruded from a spina bifida of the lower lumbar and all the sacral vertebrae. There was complete paralysis of the lower extremities. The head grew 5 cm. in one month.

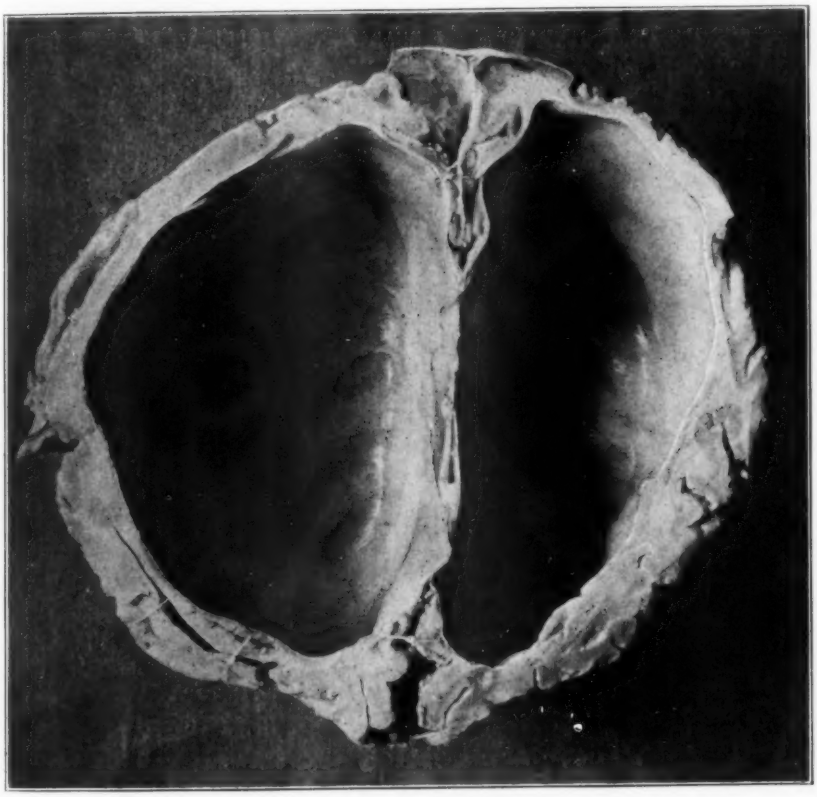

Fig. 19.—A very advanced internal hydrocephalus (Case 6, Group 1, F. W.) due to inflammatory adhesions at the base, which occluded the foramina of Magendie and Luschka.

Spinal Fluid: Clear, 3 cells per cubic millimeter. Noguchi globulin reaction negative. Reducing substance present (Fehling's).

Ventricular Fluid: Clear, 2 cells per cubic millimeter. Noguchi globulin reaction negative. Reducing substance present (Fehling's).

Tests.—1. There was very slight evidence of communication between the ventricles and the subarachnoid space in four and one-half hours. *A faint* trace of phenolsulphonephthalein was then present. 2. After ventricular introduction, phenolsulphonephthalein did not appear in the urine for sixteen minutes. *Two per cent. was excreted in two hours.* The head increased in size and at a test

after two months there *was only 1 per cent. excreted in two hours.* Phenolsulphonephthalein appeared in the urine in twenty-five minutes. At this time there was no evidence of communication between the ventricles and the subarachnoid space after three hours. 3. After subarachnoid introduction, phenolsulphonephthalein appeared in the urine in twelve minutes, and *10 per cent. was excreted in two hours.* 4. The kidney function was normal.

The patient died of hydrocephalus.

Fig. 20.—Cross-section of brain in Case 6, to show extreme ventricular enlargement, aqueduct of Sylvius patent. Dilatation of the fourth ventricle was prevented by adhesions between the dura and the cerebellum.

Pathological Findings.—The dura was firmly adherent to the cerebellum by fibrous bands, which had to be torn before the brain could be removed. These adhesions were present throughout the posterior fossa and extended almost the entire distance of the spinal canal, binding the spinal cord to the dura. The cerebellum was also firmly bound to the medulla by adhesions which occluded the foramina of exit from the fourth ventricle (Figs. 19 and 20).

The cerebral cortex was so thin that in places it was translucent. This was especially true over the temporal lobes. Here no convolutions were evident, the surface being entirely smooth. The convolutions were elsewhere flattened and the sulci shallow. Viewed from below the floor of the third ventricle appeared as a film. The third and lateral ventricles and the foramina of Monro were greatly dilated; only shreds of the septum lucidum remained. The aqueduct of Sylvius was about normal in size and everywhere patent. The fourth ventricle was compressed. The first portion of the central canal of the cord was dilated, but this soon became obliterated so that throughout its entire length there was no connection with the syringomyelocele. When the ventricles were filled, the fluid readily passed out of the central canal but not through the foramina of Luschka and Magendie. These were entirely occluded.

The corpora quadrigemina were very large. The pineal gland was small. The choroid plexus appeared normal in the gross. Microscopically the choroidal epithelium was flattened and the vascular spaces somewhat dilated.

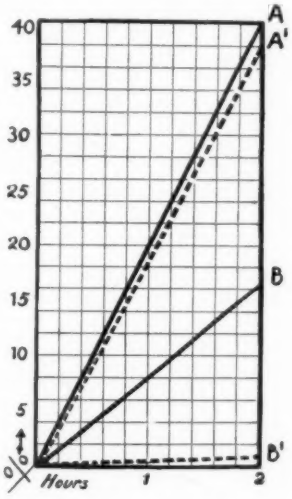

Fig. 21.—Curves comparing the normal absorption from the ventricles and the subarachnoid space with the absorption in internal hydrocephalus of the obstructive type. The base line represents a two-hour interval and the vertical line the percentage of absorption (excretion of phenolsulphonephthalein) during that time. The heavy lines represent the normal absorption and the dotted lines the absorption in hydrocephalus. *A*, normal subarachnoid absorption; *A'*, absorption from subarachnoid space of case of obstructive hydrocephalus; *B*, normal absorption of fluid placed in the ventricles; *B'*, absorption from ventricles in obstructive hydrocephalus.

Syringomyelocele and Meningocele: Two separate, non-communicating cavities were contained within the cutaneous covering. The sac protruded through a defect in the third, fourth and fifth lumbar and all the sacral vertebrae. The walls of the sac were fused in part. The meningocele was in communication with the subarachnoid space and contained clear fluid. The syringomyelocele was connected for a short distance with the central canal of the cord. This cavity contained turbid straw-colored fluid. The central canal of the cord was obliterated between the syringomyelocele and the medulla. At those points, the canal was greatly dilated. There was no communication between the cerebral ventricles and the syringomyelocele.

Remarks.—This case is unusual in that at first a very slight communication existed between the ventricles and the subarachnoid space. One month later and shortly before death there was no evident communication in three hours, and absorption following ventricular injection had diminished to 1 per cent. The time of appearance in the urine increased to twenty-five minutes.

The subarachnoid absorption was low (10 per cent.). An old inflammatory process was present obliterating all the basal foramina and tightly binding the

TABLE 5.—SUMMARY OF GROUP 1, INTERNAL—

Name and No.	Patient's Illness	Absorption after Ventricular Introduction		Absorption after Spinal Introduction		Communication, Ventricle and Subarachnoid space
		Time of appearance Minutes	Two-hour absorption Per cent.	Time of appearance Minutes	Two-hour absorption Per cent.	Time of appearance
1. P. G.	Tuberculous meningitis; internal hydrocephalus	45	0.75	6	62	None in 45 min.
2. A. H.	Internal hydrocephalus	40	1	....	....	None in 2 hrs.
3. N. P.	Internal hydrocephalus	45	1	0	0	None in 20 min.
4. N. M.	Internal hydrocephalus	40	0.50	6	35	None in 2 days
		35	0.50	....	....	.....
		40	0.50			
5. M. R.	Internal hydrocephalus	20	0.9	8	25	None in 1½ hrs.
6. F. W.	Internal hydrocephalus	16	2	12	10	Trace in less than 4½ hrs.
		25	1	....	....	None in second observation 3 hours
7. M. N.	Internal hydrocephalus	30	1.5	0	35	None in 30 min. faint trace in 14 hours

cerebellum to the medulla. This accounts for the small size of the fourth ventricle, which was unusual as the aqueduct was patent and the third and lateral ventricles were greatly dilated. On account of the strong adhesions, enlargement of the fourth ventricle was prevented. The hydrocephalus resulted from adhesions blocking the foramina of exit and preventing the cerebrospinal fluid from reaching the subarachnoid space. It must have occurred during intrauterine life as the hydrocephalus was present at birth. Whether or not the adhesions from the inflammatory process which obliterated the cisterna were responsible for the low subarachnoid absorption can only be conjectured. This case may readily be regarded as a transitional type between those with total occlusion and those with communication (Group 2).

CASE 7.—M. N., aged 5 months. Diagnosis: Internal hydrocephalus.

Clinical Note.— Past History: The patient was born at full term after a difficult instrumental delivery. The head was not noticed to be abnormally large at birth. Paralysis of the left side of the face was observed two weeks after birth. The baby had never moved his head in a normal manner, but the parents did not attribute this to any other cause than general weakness. The head had been increasing in size for about one month.

—HYDROCEPHALUS WITH OBSTRUCTION

Duration of Excretion		Etiology	Postmortem Findings
Ventricle	Spinal canal		
3% excreted in 12 hrs. Three days later the concentration of 'phthalein in the urine was undiminished	Less than 12 hrs.	Tuberculous meningitis. Meningocele present since birth	Exudate over base of brain occluding the foramina of exit.
.....	.....	Congenital; myelomeningocele also present	Occlusion of aqueduct of Sylvius.
.....	.....	Congenital	Total absence of aqueduct of Sylvius.
11 days	21 hrs.	Congenital	Living.
11 days ..... 6.1% first 24 hours. 7.5% second 24 hours. 5.7% third 24 hours.			
.....	.....	Meningitis at 4 mos. Previously normal	Absence of foramina of Luschka and Magendie. Fourth ventricle a large cyst. Marked thickening of pia arachnoid.
7 days	48 hrs.	Congenital; no history of meningitis, meningocele and syringomyelocele	Chronic inflammatory process; adhesions at base occluding foramina of exit.
.....	.....	Congenital	Living.

Physical Examination: The patient was a fairly well-nourished infant with moderate hydrocephalus. The circumference of the head was 47.5 cm. There was downward dislocation of the eyes and a nystagmus in all directions. The eye-grounds showed a marked choking of the disks, the swelling being about 3 diopters in each fundus. The left side of the face was completely paralyzed. The extremities were normal and the reflexes at the knee active. The Wassermann reaction of the blood and spinal fluid was negative.

Ventricular Fluid: Clear, 9 cells per cubic millimeter. Globulin test, negative. Fehling's test positive.

Spinal Fluid: Clear, 5 cells per cubic millimeter. Globulin test, negative. Fehling's test positive.

Tests.—1. There was no evidence of communication between the ventricles and the subarachnoid space in thirty minutes. 2. After ventricular introduction, phenolsulphonephthalein did not appear in the urine for thirty minutes. Only *1.5 per cent. was excreted in two hours.* 3. After subarachnoid introduction, *35 per cent. phenolsulphonephthalein was excreted in two hours.*

Remarks.—From the results of the foregoing observations we know that there was an obstruction to the outflow of cerebrospinal fluid from the ventricles into the subarachnoid space. The excretion of phenolsulphonephthalein from the subarachnoid space (35 per cent.) was normal.

SUMMARY OF GROUP 1

The essential feature of this type of internal hydrocephalus is the absence of communication between the ventricles and the subarachnoid space. This lack of communication was demonstrated clinically in seven patients. It was confirmed at necropsy in five. In one (Case 1, P. G.) a thick tuberculous exudate covered the base of the brain and tightly sealed the communicating foramina. In two (Case 5, M. R., and Case 6, F. W.) the basal foramina were occluded by adhesions resulting from an old meningitic process; in the former, the illness occurred four months after birth, and in the latter it was evidently prenatal. In two there was complete occlusion of the aqueduct of Sylvius. In one of these (Case 2, A. H.) epithelial remnants of the aqueduct were demonstrated microscopically; in the other (Case 3, N. P.) no trace of the aqueduct was present. In both the region of the aqueduct was occupied by neuroglia tissue. The sixth and seventh patients are living (Case 4, N. M., and Case 7, M. N.). In these seven patients the absorption from the ventricle was less than 1 per cent. in six. In the one in whom the absorption was as high as 2 per cent., there was probably a minute communication between the ventricles and the subarachnoid space. At a subsequent examination the absorption in this case was less (1 per cent.), and there was proof of the obliteration of the foramina. The absorption from the ventricles is independent of the size of the ventricles or the amount of the contained cerebrospinal fluid. In Case 1 (P. G.) the ventricles were only moderately dilated and the absorption was not greater than in the most distended ventricles. The excretion of phenolsulphonephthalein in the urine is prolonged in this group (from the normal period of several hours, to ten days). The time of appearance of the dye in the urine is greatly delayed also (from thirty to fifty minutes).

In marked contrast to the negligible ventricular absorption was the high subarachnoid absorption in all except the two postmeningitic cases (Cases 5 and 6). The appearance time in the urine and the duration of excretion following subarachnoid injections were normal.

This type of internal hydrocephalus results because the cerebrospinal fluid cannot escape from its place of origin in the ventricles,

where the absorption is negligible, to the subarachnoid space, where the absorption normally occurs, because the channels of communication are occluded (Fig. 21).

GROUP 2.—INTERNAL HYDROCEPHALUS WITH FREE COMMUNICATION BETWEEN THE VENTRICLES AND THE SUBARACHNOID SPACE

CASE 8.—R. G., aged 1½ years. Diagnosis: Internal hydrocephalus.

Clinical Note.—Family History: Three other children living and well. No history of syphilis or hydrocephalus.

Past History: Full term. Weight at birth, 12 pounds. Spontaneous delivery. Patient held up head at the fourth month, sat up at the sixth month. Dentition began at the seventh month. He appeared a normal baby in every respect until 7 months of age.

Present Illness: When 7 months of age, he became ill with high fever, vomiting, great irritability and muscular rigidity. This condition lasted for three days and during the following two weeks he had an irregular fever. The appetite was poor and he lost in weight. After this illness the patient was unable to hold up his head. One month later it was noticed that the head was larger than normal and that the eyes were pushed downward. For the next three months, the head continued to increase rapidly in size.

Examination: The patient was a well-developed and well-nourished infant. The head measured 52 cm. in circumference. He was unable to raise his head. The child saw and heard and recognized the members of his family. The forehead was prominent and the occiput flattened. The anterior fontanel was widely open and the sutures separated. The eyes were displaced downward and there was weakness of both external recti. The eye-grounds were normal. The reflexes were active and equal; a bilateral ankle clonus was present.

Spinal Fluid: Clear, 6 cells per cubic millimeter. Noguchi globulin test, negative.

Ventricular Fluid: Clear, 6 cells per cubic millimeter. Noguchi globulin test, negative.

Tests.—1. There was communication between the ventricles and the subarachnoid space. Phenolsulphonephthalein was demonstrated in the spinal fluid *two minutes* after ventricular introduction. The test was repeated after one month and phenolsulphonephthalein appeared in the spinal fluid in one minute. 2. After ventricular introduction phenolsulphonephthalein appeared in the urine in thirty minutes and *2 per cent. was excreted in two hours.* One month later, the test was repeated and phenolsulphonephthalein appeared in the urine in twenty minutes and 2.3 per cent. was excreted in two hours. 3. After subarachnoid introduction, *11 per cent. of phenolsulphonephthalein was excreted in two hours.* At the second test, phenolsulphonephthalein appeared in the urine in thirteen minutes and 7 per cent. was excreted in two hours.

Remarks.—From the history it seemed very definite that an attack of meningitis was the etiological factor responsible for the development of the internal hydrocephalus. From the rapid passage of fluid from the ventricles to the subarachnoid space it was evident that free communication existed. The absorption from the subarachnoid space was much diminished, from 7 to 11 per cent. of phenolsulphonephthalein, as opposed to the normal of 35 per cent. or over. The appearance of the dye in the urine following its introduction into the ventricles and into the subarachnoid space was also much delayed. The kidney function test was normal.

CASE 9.—M. R., aged 11 months. Diagnosis: Cerebrospinal meningitis with secondary internal hydrocephalus.

Clinical Note.—Family History: No history of syphilis or hydrocephalus.

Past History: Only child, full term, normal delivery; breast fed. Dentition began at fourth month. Sat up at eight months. Always well until present illness.

Present Illness: This began suddenly three days before admission to the outpatient department (March 31, 1913) with high fever, drowsiness, vomiting and extreme irritability. She had had one convulsion. Temperature 101.6 F.

The following note was made: "An irritable colored girl, aged 11 months, appears very sick. She is well-nourished and well-developed. There is slight cervical rigidity. The sudden onset, drowsiness, fever, vomiting, convulsion and rigidity of the neck suggest meningitis." Lumbar puncture was not allowed and hospital treatment was refused by the parents. The first two weeks after the onset the baby was very sick. About April 12 she was unconscious for five days. Two weeks later (April 26, 1913) she vomited and began to have twitching movements of the face and extremities.

On admission to the hospital (May 2, 1913) the child, greatly emaciated, was in a stupor from which it was difficult to arouse her. The head measured 45 cm. in circumference, the anterior fontanel was small. The pupils reacted slowly to light. Vision was evidently impaired. There was rigidity of the extremities, exaggerated reflexes and ankle clonus. Temperature, 102 F. Leukocytes, 14,400. Von Pirquet test, negative.

Spinal Fluid: Twenty c.c. turbid fluid. Noguchi globulin reaction, positive; culture showed no growth. Smear: Many pus cells, no organisms.

Thirteen c.c. of antimeningitic serum were injected. The patient was removed from the hospital by her parents after twenty-four hours. The child was brought to the dispensary seven weeks later (June 25, 1913) because she could not see. On examination in the ward, July 5, 1913, the patient was poorly nourished, apparently blind, and very sensitive to sounds. The head was retracted and the neck rigid and there was spasticity of the extremities. The head measured 45 cm. in circumference. The pupils were unequal and reacted only slightly to light. There was no choking of the disks. There was a vertical and lateral nystagmus. Kernig's sign was positive. The reflexes were exaggerated and a bilateral ankle clonus was present. Temperature, 98.6 F. Leukocytes, 12,000. Wassermann reaction, negative.

Spinal Fluid: Clear, 10 c.c. Forty-two cells per cubic millimeter; Noguchi globulin reaction, positive; cultures negative; tubercle bacilli not found.

Ventricular Fluid: Clear fluid, 12 cells per cubic millimeter; Noguchi globulin reaction, positive.

The child was taken home after a few days, having made no improvement.

Tests.—1. There was communication between the ventricles and the subarachnoid spaces. Phenolsulphonephthalein appeared in the spinal subarachnoid space *seven minutes* after being introduced into the ventricle. 2. After ventricular introduction, phenolsulphonephthalein appeared in the urine in thirteen minutes and *6.5 per cent. was excreted in two hours.* Later (two and one-half months) a second test was made and phenolsulphonephthalein appeared in the urine in twenty minutes and only *0.5 per cent. was excreted.* 3. After subarachnoid introduction, phenolsulphonephthalein appeared in the urine in eight minutes and *14 per cent. was excreted in two hours.* Two days later this test was repeated and 9.5 per cent. of phenolsulphonephthalein was excreted in two hours. It was being excreted in the urine after seventy-two hours. 4. The kidney function was normal.

Remarks.—The child was seen at the onset of an attack of epidemic cerebrospinal meningitis. A month afterward she was brought to the hospital because of beginning blindness. The absorption after ventricular injection was low (about 50 per cent. of the normal). The patient was admitted to the hospital two months after the onset, totally blind, and hydrocephalus was evident. There was very marked diminution in absorption, only 0.5 per cent. after ventricular injection and 9.5 per cent. and 15 per cent. from the subarachnoid

space. Free communication existed between the ventricles and the subarachnoid space.

CASE 10.—H. N., aged 8 months. Diagnosis: Internal hydrocephalus.[4]

Clinical Note.—Family History: No other cases of hydrocephalus in the family.

Examination: The child was well-nourished. The head measured 51 cm. in circumference. The anterior fontanel measured 10 by 8 cm.; it was tense and slightly bulging. There was a bilateral choked disk. The knee-reflexes were exaggerated though equal. Two and one-half weeks after the first admission the patient's head had increased 2 cm. in size. During another interval of eighteen days the head increased 0.9 cm. in circumference. At this time lumbar puncture was repeatedly done and fluid withdrawn for its therapeutic effect. Following this mode of treatment the child became able to hold up its head and the increase in size became less rapid. The Wassermann test was negative for the blood and the ventricular and spinal fluids. Von Pirquet test, negative.

Ventricular Fluid: Clear, 6 cells per cubic millimeter. Noguchi globulin test, negative.

Spinal Fluid: Clear, 6 cells per cubic millimeter. Noguchi globulin test negative.

Tests.—1. Communication was demonstrated between the ventricles and the subarachnoid space. Phenolsulphonephthalein appeared in the spinal fluid *twenty minutes* after its introduction into the ventricle. 2. Phenolsulphonephthalein appeared in the urine twenty-five minutes after its introduction into the ventricles *and 4.4 per cent. was excreted in two hours.* Two weeks later, the absorption was 4 per cent. 3. The absorption from the subarachnoid space *was 10 per cent. during a two-hour period.* The same result was obtained two weeks later. 4. The kidney function test was normal.

Remarks.—Except for the brief illness shortly after birth there was nothing to suggest a cause for the hydrocephalus. We were unable to obtain any information either from the mother or the attending physician to warrant a diagnosis of meningitis. The clinical tests showed that there was a delayed absorption from the subarachnoid space. The time of appearance in the spinal canal following the ventricular injection was much longer than in either of the two preceding cases of this group. That there was adequate communication, however, was shown by the relatively high concentration of phenolsulphonephthalein in the spinal fluid two and one-half hours after the ventricular injection.

CASE 11.—J. C., aged 16 months. Diagnosis: Internal hydrocephalus.

Clinical Note.—Only child. Parents, healthy; instrumental and prolonged labor (thirty-one hours). A cephalhematoma developed soon after birth and disappeared in five weeks. The primary respirations were difficult to establish. No convulsions. The enlargement of head was not noticed at birth. The head appeared large when he was 3 months of age and thereafter steadily increased in size. In six weeks it increased 2 inches, and in two weeks ¾ inch. January, 1913, the head measured 55.5 cm.; September, 69.5 cm., and November, 1913, 72.5 cm. The child never had fever or convulsions or any illness suggesting meningitis.

Examination: The head was large and measured 72 cm. in circumference. The reflexes were exaggerated. The Wassermann reaction of the spinal fluid and blood was negative.

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7. The phenolsulphonephthalein tests in this case demonstrated a communicating type of hydrocephalus. Repeated lumbar punctures were made for their therapeutic effect. The process has remained stationary for three months and the child is apparently cured.

By lumbar puncture from 40 to 75 c.c. of clear fluid were obtained. Six cells per cubic millimeter. Globulin test, negative. Fehling's, slight reduction.

Tests.—1. There was communication between the ventricles and subarachnoid space. Phenolsulphonephthalein appeared in the spinal fluid in less than one minute after its introduction in the ventricle. 2. The absorption following the introduction of phenolsulphonephthalein in the ventricles was 4 per cent. in two hours and the time of appearance in the urine was forty minutes.

Remarks. A subarachnoid test was not obtained. It was evident, however, from the rapid appearance of phenolsulphonephthalein in the subarachnoid space that communication was adequate.

SUMMARY OF CASES IN GROUP 2

In this type of hydrocephalus the communication between the ventricles and the subarachnoid space is patent, thus differing from Type 1, in which there is no communication between the ventricles and the

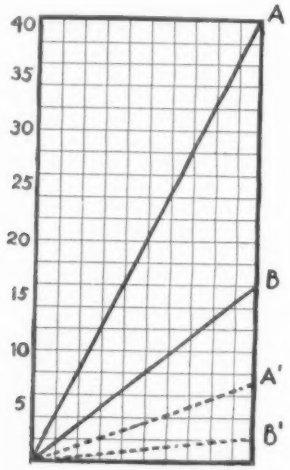

Fig. 22.—Curve comparing the normal ventricular and subarachnoid absorption with the absorption in internal hydrocephalus of the communicating type. The base line represents a two-hour period and the vertical line represents the absorption (percentage of phenolsulphonephthalein excreted) during this time. The heavy lines represent the normal absorption and the dotted lines the absorption in hydrocephalus. *A*, normal subarachnoid absorption; *A'*, absorption from subarachnoid space in communicating hydrocephalus; *B*, normal absorption of fluid placed in the ventricles; *B'*, absorption of fluid placed in ventricles of communicating hydrocephalus.

subarachnoid space. Following intraventricular introduction of phenolsulphonephthalein, the dye appears almost immediately (from one to seven minutes) in the spinal fluid. In one case of this group on two separate occasions the time of appearance in the spinal fluid was delayed to fifteen and twenty minutes. We were unable to determine the reason for this delay. Communication in this type of hydrocephalus is further proved by the rapid appearance in the ventricular fluid of

phenolsulphonephthalein after being introduced into the subarachnoid space.

The absorption from the subarachnoid space of these patients is greatly diminished (about 10 per cent. in two hours). There is a corresponding increase in the time of first appearance of phenolsulphonephthalein in the urine and in the time required for its total excretion from the subarachnoid space. *The diminished subarachnoid absorption is the factor responsible for the production of the internal hydrocephalus* (Fig. 22).

The absorption after ventricular injection was also very low (about 4 per cent.), but distinctly higher than in Group 1. *Since it has been shown that there is practically no absorption from the ventricles, the absorption following ventricular injection in normal cases or in cases of internal hydrocephalus of the communicating type must be due to absorption from the subarachnoid space after the fluid* has passed through the foramina of exit from the ventricles.

We have had no pathological examination on patients with hydrocephalus of this type demonstrated by these clinical tests. It is very likely that the diminished absorption from the subarachnoid space is due to adhesions which diminish the size of the subarachnoid space. Adhesions anterior to the foramina of Luschka, by causing obliteration of the cisterna magna, would prevent the passage of fluid into the general cerebral subarachnoid space as effectually as if the aqueduct of Sylvius were obliterated. The two groups would then be essentially similar, differing only in the fact that the spinal subarachnoid space participated in absorption in the communicating type. When there are adhesions at the base of the brain they are frequently present also between the cord and the meninges.

We have had the opportunity of examining the specimen from a patient who had hydrocephalus of this variety. There was a congenital internal hydrocephalus evidently the result of an intra-uterine meningitis. Dense adhesions were found along the cord and the base of the brain obliterating the cisterna magna. The foramen of Magendie was sealed by adhesions, but the foramina of Luschka were patent and greatly dilated. There was no cisterna for the reception of fluid.

How much alteration in the meninges alone, without adhesions, interferes with absorption, cannot be stated. It seems to us probable that the major part if not all of the disturbaance is due to the limitation of the subarachnoid space.

That there is another type of hydrocephalus intermediate between Group 1 and Group 2 appears probable. There must be cases in which the obstruction to the outflow of fluid from the ventricles is not complete but partial, and in which the subarachnoid absorption is either

normal or diminished. With such a combination a hydrocephalus must also result. Indeed, Case 6 (Group 1, F. W.) probably belongs to this intermediate group. That there was a slight communication was shown by the trace of phenolsulphonephthalein in the spinal fluid after ventricular introduction. The subarachnoid absorption was greatly diminished and corresponded in amount with the absorption found in the cases of Group 2. The slightly higher absorption, 2 per cent. after ventricular introduction, is probably also to be explained by a partial communication. At a later observation a complete obstruction was found and the ventricular absorption was much less.

10. CLINICAL DIFFERENCES BETWEEN THE COMMUNICATING AND OBSTRUCTIVE TYPES OF INTERNAL HYDROCEPHALUS

There is no way by which a differentiation can be made between the obstructive and the communicating types of internal hydrocephalus except by the actual determination of the presence or the absence of communication between the ventricles and the subarachnoid space. While the increase in size of the head appears usually to be slower in many cases in which there is communication, there are other cases in which the increase is very rapid.

It is sometimes possible to tell by the large amount of fluid removed by lumbar puncture that the case is of the communicating type. This can be, however, only when the internal hydrocephalus is advanced in degree. When there is obstruction either at the aqueduct of Sylvius or at the foramina of Luschka and Magendie, 25 c.c. or more of fluid can frequently be obtained by lumbar puncture and the erroneous conclusion might be reached that the fluid was withdrawn from the ventricles. Differences in the cell count and in serological tests, between the spinal and ventricular fluids, are usually too slight to be of any value.

The only satisfactory method of differentiating these two groups is by the phenolsulphonephthalein test as described above.

11. THE RELATION OF OBSTRUCTION TO INTERNAL HYDROCEPHALUS

That obstruction may be responsible for internal hydrocephalus was first demonstrated by Magendie. John Hilton accepted Magendie's views and thought that probably every case was so produced. In his excellent lectures on "Rest and Pain," drawings are given to show the obstruction which he found quite constantly. Quincke, Bourneville and Noir, Spiller, Browning, Schlapp and Géré, Neurath and numerous other writers reported cases showing various types of occlusion which were held responsible for the internal hydrocephalus. Obstruc-

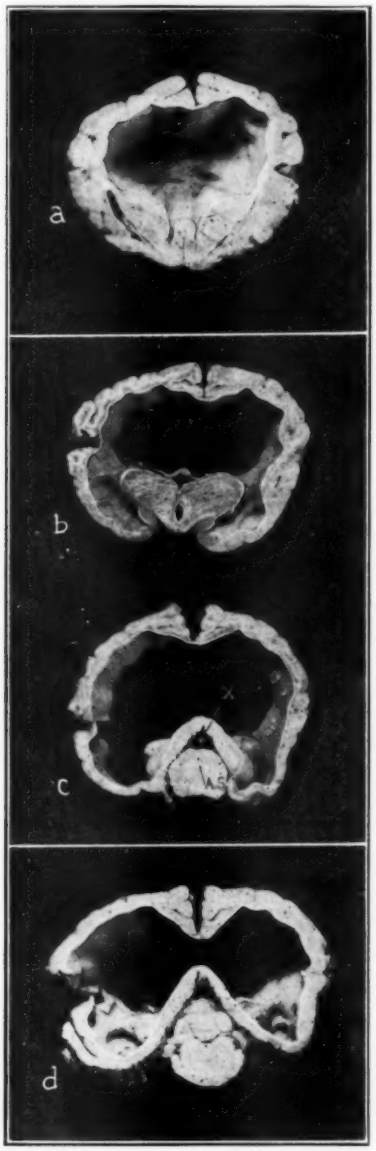

Fig. 23.—Spontaneous internal hydrocephalus in a dog found by Dr. A. P. Jones. The aqueduct of Syivius (*A. S.*) is completely occluded. The lateral venticles form a single cavity owing to the absorption of the septum lucidum. A free communication is present between the third ventricle and the subdural space at *X*, but the hydrocephalus is not modified owing to the poor absorption from the subdural space. Note the small fourth ventricle posterior to the obstruction.

tions have been observed at the foramina of Monro producing a unilateral hydrocephalus, at the aqueduct of Sylvius producing dilatation of the third and lateral ventricles, and at the foramina of Luschka and Magendie producing enlargement of all the ventricles. The obstructions have been due to inflammations, tumors and congenital defects. Obstructions have also been noted in animals, especially in the horse, cow, dog and cat (Fig. 23). Dexler studied many cases of hydrocephalus, known as *Dummkoller,* in the horse, and found quite constantly an occlusion of the foramina of Luschka. It will be recalled that the foramen of Magendie does not exist in the horse.

In our series of seven patients in whom an obstruction was determined by the phenolsulphonephthalein test, necropsies were obtained in five, and in each of these the presence of an obstruction was demonstrated. Moreover, an obstruction experimentally placed in the aqueduct of Sylvius causes an internal hydrocephalus. Internal hydrocephalus is produced because the fluid forms in the ventricles and cannot escape to the subarachnoid space where it is absorbed. In this respect there is a close analogy between the ventricles of the brain and the renal pelvis. Just as hydronephrosis results from obstruction along the course of the ureter, so a hydrocephalus results from an occlusion of the channels of exit from the ventricles. In neither the pelvis of the kidney nor the ventricles of the brain is there sufficient absorption to overcome the effects of occlusion.

12. THE RELATION OF MENINGITIS TO INTERNAL HYDROCEPHALUS

In two specimens (Group 1) it was shown after the pathological examination that adhesions occluding the communicating foramina were responsible for the hydrocephalus. These were undoubtedly the result of a previous meningitis. In Group 2, two patients gave a definite history of meningitis, immediately preceding the onset of the internal hydrocephalus. Case 9 (M. R.) of Group 2 was seen during an attack of epidemic meningitis and during the subsequent development of the hydrocephalus. Case 8 (R. G.), Group 2, gave a typical history of meningitis. Before this illness the child was perfectly well and afterward he was not able to hold up his head and his head had enlarged.

Case 6 of Group 1 was an example of congenital hydrocephalus with a meningocele. Post-mortem examination, however, revealed the evidences of a marked basilar meningitis with occlusion of the foramina of Luschka and Magendie. There is, therefore, clinical and pathological evidence that meningitis is frequently the etiological factor in the production of internal hydrocephalus of both the obstructive and the communicating types, and there is every reason to believe that it occurs both before and after birth.

That meningitis is an important factor in the production of this disease has been clinically recognized at least since the beginning of the nineteenth century. Alexander Monro (1827) observed that hydrocephalus apparently of postnatal origin was frequently preceded by a severe illness, which was not then recognized as meningitis. Greater attention was directed to this disease as an etiological factor by Trousseau (1857), Foerster (1863), Ziemsen and Hess (1874). Joslin, Koplik, Gildesheim, Barlow and Lees, and Göppert recently called attention to the importance of this disease as a cause of internal hydrocephalus.

The pathological changes reported by various observers have not been uniform. Barlow and Lees, Hildesheim, and Bettencourt and Franca believe that the process always occluded the foramina of Magendie and Luschka. Barlow and Lees observed only two cases in a large series in which no occlusion was found and thought the hydrocephalus in these cases was due to an overproduction of fluid. Göppert, from post-mortem examination of twenty-three cases, classified the anatomical findings under three types: (1) total occlusion, four cases; (2) foramen of Magendie closed, but the foramina of Luschka large, six cases; (3) all the foramina patent, thirteen cases. Göppert's determination of the patency or occlusion of these openings was made by granular injections into the ventricles post mortem. The results of most observers have been based on inspection of the base of the brain, from which it is impossible to determine the condition of the foramina with certainty.

Why an internal hydrocephalus should result with patent foramina has never been demonstrated. We are unable to give the pathological basis for hydrocephalus of the communicating type owing to the fact that all of our patients are living; but the evidence here presented gives an explanation for the production of this type of hydrocephalus.

13. THE RELATION OF VENOUS STASIS TO INTERNAL HYDROCEPHALUS

Venous stasis due to obstruction of the small or the large veins of Galen is undoubtedly the cause of a small percentage of the cases of internal hydrocephalus. Experimental proof of this has been given. Internal hydrocephalus resulting from thrombosis by these veins has also been reported. Although such a cause of hydrocephalus is infrequent, it should always be looked for post mortem. It is also possible that tumors in the region of the midbrain might exert sufficient pressure to obstruct either the aqueduct or the veins of Galen. We are inclined to regard venous stasis as being of relative minor importance in the production of hydrocephalus.

Certainly in very young children tumors are uncommon, and the obstructive process is usually insufficient to produce a simultaneous involvement of the veins. In adults, among whom tumors are more common, it may play a more frequent but always a subsidiary rôle, because the aqueduct of Sylvius will usually also be occluded.

14. THE POSSIBILITY OF OTHER CAUSES OF INTERNAL HYDROCEPHALUS

Almost every conceivable cause, direct and indirect, has been suggested as being responsible for hydrocephalus. Alcohol, rickets, trauma, tuberculosis, syphilis, heredity, psychic disturbance during

TABLE 6.—SUMMARY OF GROUP 2, INTERNAL—

Case	Illness	Absorption after Ventricular Introduction		Absorption after Spinal Introduction		Communication between Ventricular and Subarachnoid space
		Time of appearance Minutes	Two-hour absorption Per cent.	Time of appearance Minutes	Two-hour absorption Per cent.	Time of Appearance in Spinal Canal following Ventricular Introduction—Minutes
8. R.G.	Internal hydrocephalus	30	2.	Not obt.	11	1
		20	2.3	13	7	2
9. M.R.	Internal hydrocephalus following epidemic meningitis	13-15	6.5	.....	.....	7 —
	Two months later	20	0.5	8	14	2
				Not obt.	9.5	
10. H.N.	Internal hydrocephalus	25	4.4	Not obt.	10	20
		About 25	4	Not obt.	10	13
11. J. C.	Interanl hydrocephalus	30	4	0	0	1

* No post-mortem examination in any case.

pregnancy, lack of resistance of the brain tissue, osteogenetic defects of the skull and many other less likely possibilities have been suggested. Syphilis is undoubtedly responsible for a certain number of cases, but to cause hydrocephalus, syphilis must produce a lesion which involves the cerebrospinal spaces and cause a diminished absorption of cerebrospinal fluid either by occlusion of the foramina or by an affection of the meninges. In not one of our cases was there any evidence by serelogical test that syphilis was the etiological factor. Elsner thought syphilis responsible in three cases out of eighteen, and Hedenfeld in

10 per cent. of his cases. It is very unlikely that as systemic diseases without localized manifestations syphilis, tuberculosis, rickets and alcoholism have any etiological bearing on the production of internal hydrocephalus.

There was no familial or hereditary history of hydrocephalus in our cases. Göhlis reports an instance of a woman who gave birth to six still-born, hydrocephalic children.

The production of hydrocephalus by trauma is very difficult to prove. We have seen one case (not here recorded) in which the father, who was a physician, insisted that the onset of the disease dated

—HYDROCEPHALUS WITHOUT OBSTRUCTION *

Duration of excretion after		Kidney function 2 hours Per cent.	Etiology
Ventricular introduction	Spinal introduction		
Longer than 2 days	0	44	Definite history of meningitis. Hydrocephalus followed immediately.
.....	More than 24 hrs.	40 (1st hr.)	Followed meningitis.
.....	.....		
.....	.....	45	Hydrocephalus noted 6 weeks after birth. May have resulted from illness 3 days after birth.
0	0	Not tested.	

from a severe fall. Various congenital anomalies have been associated with hydrocephalus, such as hydrothorax, absence of kidney, cleft palate, bicornuate uterus, etc. The occurrence of internal hydrocephalus with spina bifida has been frequently noted. There were three such instances present in our series of cases.

Lack of resistance of cerebral tissue and imperfect development of the skull, though frequently suggested as causes of hydrocephalus, have been mentioned merely as possibilities. The cerebral atrophy and non-union of the sutures of the skull are undoubtedly secondary manifestations of the intracranial pressure.

15. INTERNAL HYDROCEPHALUS FOLLOWING THE REMOVAL OF A MENINGOCELE

Internal hydrocephalus following the extirpation of a meningocele has been frequently reported, but the cause for its development has never been satisfactorily explained. Muscatello, who has reported a series of cases of this character, attributed the hydrocephalus to an operative infection. His reason for doing this was based on the frequency with which ulceration of the meningocele was observed.

From our observations on the general character of absorption of fluid from the subarachnoid space, it is most likely that the hydrocephalus results from a diminution in the absorption of the cerebrospinal fluid. This diminished absorption takes place because a large part of the absorbing surface is removed at the time of the operation.

Before removing a meningocele, it is important to determine the absorption from the subarachnoid space in order to determine whether or not it is sufficient. If absorption is below the normal, operation in the light of our present knowledge would be contra-indicated.

16. SUGGESTIONS AS TO THE TREATMENT OF INTERNAL HYDROCEPHALUS

We have shown that there are two types of internal hydrocephalus differing physiologically and anatomically, and it is obvious that an entirely different therapy is necessary for each variety. In the treatment it is important to know which type of hydrocephalus is present — the obstructive or the communicating. This can be determined by the phenolsulphonephthalein test.

In the obstructive type of internal hydrocephalus, the treatment should be directed toward removal of the obstruction. If this is at the foramina of Magendie and Luschka, as in Cases 5 and 6 of Group 1, the obstruction without doubt could be relieved. If the occlusion is located at the aqueduct of Sylvius, as in Cases 2 and 3 of Group 1, the problem of making an opening is obviously more difficult, perhaps impossible. It would also be necessary, before undertaking such an operation, to determine the amount of absorption from the subarachnoid space. If there is a low subarachnoid absorption as in Case 6 of Group 1, it is probable that the relief of the obstruction would merely transform an internal hydrocephalus of the obstructive type into one of the communicating type.

In the communicating type, the internal hydrocephalus is the result of diminished absorption from the subarachnoid space. In one case the post-mortem findings indicated that adhesions from an old inflammation produced obliteration of the cisterna magna and prevented the

cerebral subarachnoid space from participation in the absorption. At present, the rational treatment in this type of hydrocephalus would be to drain the fluid into other tissues where there is adequate absorption.

17. SUMMARY AND CONCLUSIONS

An internal hydrocephalus was experimentally produced in dogs by placing an obstruction in the aqueduct of Sylvius.

It is therefore evident that the cerebrospinal fluid is formed in the ventricles faster than it can be absorbed, and that the aqueduct of Sylvius is essential for its escape.

An internal hydrocephalus resulted from placing an obstruction in the aqueduct of Sylvius in spite of the extirpation of the choroid plexus of both lateral ventricles. This procedure apparently modifies the grade of the internal hydrocephalus.

An internal hydrocephalus may also result from an experimental ligation of the vena Galena magna near its origin; when the ligature is more distally placed or when the sinus rectus alone is ligated, an internal hydrocephalus does not result, owing to the efficient venous collateral circulation.

Cerebrospinal fluid is derived mainly from the choroid plexuses, probably both by filtration and by secretion.

An increase of cerebrospinal fluid is caused by general venous congestion as demonstrated by temporary jugular compression. This increase of fluid ceases when the congestion is relieved by the collateral circulation.

Drugs and glandular extracts produce but slight change in the rapidity of formation of cerebrospinal fluid. Pilocarpin produced a slight increase.

There is a definite impermeability of the fluid-forming structures. Of the various substances in solution in the blood, only traces of a few find their way into the cerebrospinal fluid. The cerebrospinal fluid is more strongly protected from substances in the blood than the peritoneal, pleural and pericardial fluids.

There is a rapid and constant formation and absorption of cerebrospinal fluid. A new supply is formed and absorbed at least every four to six hours.

The lymphatics play a negligible part in the absorption of cerebrospinal fluid.

Cerebrospinal fluid is absorbed directly into the blood. Absorption is from the entire subarachnoid space. It is a diffuse process and does not take place through specialized structures such as the pacchionian granulations or through stomata opening into the venous sinuses. That

stomata do not exist is demonstrated by the fact that granules do not readily pass from the subarachnoid space into the blood.

There is practically no absorption from the ventricles.

The maintenance of an equilibrium between the formation and the absorption of cerebrospinal fluid necessitates a communication between the ventricles and the subarachnoid space.

Communication is solely by the foramina of Magendie and Luschka.

After the introduction of phenolsulphonephthalein into the subarachnoid space it soon appears in the lateral ventricles. There are therefore no valves at these openings.

If an obstruction exists at the aqueduct of Sylvius, phenolsulphonephthalein does not appear in the spinal fluid. The so-called foramina of Mierzejewsky and Bichat therefore do not exist.

Granules placed in the subarachnoid space, without pressure, are soon uniformly distributed throughout the entire spinal and cerebral subarachnoid space. There is no evidence of a current to the region of the venous sinuses. Granules pass along the olfactory and optic nerves, over the gasserian ganglion of the trigeminal nerve and a short distance along the auditory nerves, but not along the remaining cranial and spinal nerves.

Internal hydrocephalus can be divided into two anatomically different types, depending on the patency or occlusion of communication between the ventricles and the subarachnoid space.

In seven patients with internal hydrocephalus lack of communication was demonstrated clinically. In each of these seven cases there was practically no absorption from the ventricles, while the subarachnoid absorption was high. The internal hydrocephalus, therefore, resulted because the passage of fluid from the ventricles into the subarachnoid space was prevented.

Four cases of internal hydrocephalus in which there was communication between the ventricles and the subarachnoid space were studied. In these cases there was a low subarachnoid absorption. Meningitis was the cause of the hydrocephalus in two patients with the obstructive type and two with the communicating type of hydrocephalus.

The probable cause of internal hydrocephalus following the excision of a meningocele is the limitation of absorbing surface and consequent diminution in the absorption of cerebrospinal fluid.

Surgical treatment differs according to the variety of internal hydrocephalus. *In the obstructive type* the obstruction must be removed. *In the communicating type* it is necessary to increase the area for the absorption of fluid.

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